FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

June 9, 2021

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the committee's advice. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division, Office, or Agency.

Table of Contents

I. Introduction

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements).

A. Bulk Drug Substances That Can Be Used by Compounders under Section 503A

One of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that meet one of the following criteria:

> (1) Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapters on pharmacy compounding;
> (2) If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
> (3) If such a monograph does not exist and the drug substances are not components of drugs approved by the Secretary, appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.

(*See* section 503A(b)(1)(A)(i) of the FD&C Act.)

FDA is considering those substances nominated for inclusion on the list of bulk drug substances that can be used to compound drug products under section 503A of the FD&C Act (503A Bulks List). In the *Federal Register* of February 2019, FDA published notice of a final rule establishing the criteria for evaluation of bulk drug substances for inclusion on the 503A Bulks Lis (84 FR 4696):

(1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;

(3) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and

(4) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

In evaluating the candidates for the 503A Bulks List under these criteria, the Agency will use a balancing test. Specifically, the Agency will consider each criterion in the context of the others and balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the list.

B. Withdrawn or Removed List

1. Process for Identifying Candidates for or Amendments to the Withdrawn or Removed List

Under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA is to develop a list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective (the Withdrawn or Removed List (codified at 21 CFR § 216.24)).

The following outlines the process that has been and will be used in the future to identify new candidates for this list, or to identify proposed amendments to the list, such as removing an entry or amending an entry on the list to qualify it in some way because the drug has been shown to be safe and effective for some use.

FDA stated in a final rule published in the October 7, 2016 *Federal Register* that FDA intends to continue updating the Withdrawn or Removed List through notice and rulemaking (see 81 FR 69668).

Process for Identifying Candidates For or Amendments to the List:

- FDA periodically reviews available information to identify and compile a list of possible new candidate drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. The information may include, for example, *Federal Register* notices announcing withdrawal of approval of a

drug application for safety or effectiveness reasons, *Federal Register* notices announcing an Agency determination that a drug product was removed from sale for reasons of safety or effectiveness, relevant FDA Alerts, FDA Drug Safety Communications, FDA News Releases, Public Health Advisories, Dear Healthcare Practitioner Letters, Citizen Petitions, and Sponsor letters.

- In addition, periodically, FDA reviews available information to determine whether any new drug applications have been approved for a drug product containing as an active ingredient any of the drugs on the list to determine whether any of the drug entries on this list should be modified to account for this new safety and effectiveness determination and approval. For example, if a drug has been approved in a new formulation, indication, route of administration or dosage form since the list was last revised, FDA might consider proposing a modification to the list to remove the drug from the list or to exclude the particular formulation, indication, route of administration, or dosage form.

- Appropriate divisions within the Office of New Drugs (OND) then evaluate each identified candidate or proposed modification using the available information about the drug and prepare a review of the information that documents their recommendations as to whether to include the drugs on the Withdrawn or Removed List or remove a drug or modify an entry.

- We intend to propose regulations to revise the Withdrawn or Removed List periodically, as appropriate, as we identify drugs that we tentatively determine should be listed. We would also propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing, for example, if some version of a drug on the list has been approved for marketing.

2. Entry Under Evaluation for the Withdrawn or Removed List

The Agency is considering "Neomycin Sulfate: All parenteral drug products containing neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder)" for inclusion on the Withdrawn or Removed List. See Tab 5 for the background material that forms the basis for FDA's proposal to include this entry on the list.

II. Substances Nominated for Inclusion on the 503A Bulks List (in order of discussion at the meeting)

A. Melatonin (Tab 1)

1. Nominations (**Tab 1a**)
    a. National Community Pharmacists Association
    b. Professional Compounding Centers of America
    c. Technology and Business Law Advisors, LLC

2. Nomination Clarification (**Tab 1b**)
    a. Professional Compounding Centers of America

3. FDA Evaluation (**Tab 1c**)

B. Methylcobalamin (Tab 2)

1. Nominations (**Tab 2a**)
    a. Alliance for Natural Health USA
    b. American Association of Naturopathic Physicians
    c. American College for Advancement in Medicine
    d. Fagron
    e. Integrative Medicine Consortium
    f. International Academy of Compounding Pharmacists
    g. McGuff Compounding Pharmacy Services, Inc.
    h. National Community Pharmacists Association
    i. Professional Compounding Centers of America

2. Nomination Clarification (**Tab 2b**)
    a. Alliance for Natural Health USA
    b. Joint clarification from American Association of Naturopathic Physicians and Integrative Medicine Consortium
    c. Joint clarification from Fagron, International Academy of Compounding Pharmacists, National Community Pharmacists Association, and Professional Compounding Centers of America
    d. McGuff Compounding Pharmacy Services, Inc.

3. FDA Evaluation (**Tab 2c**)

C. Choline Chloride (Tab 3)

1. Nominations (**Tab 3a**)
    a. Alliance for Natural Health USA
    b. American Association of Naturopathic Physicians
    c. American College for Advancement in Medicine
    d. Integrative Medicine Consortium
    e. International Academy of Compounding Pharmacists
    f. McGuff Compounding Pharmacy Services, Inc.

2. Nomination Clarification (**Tab 3b**)
    a. Alliance for Natural Health USA
    b. Joint clarification from American Association of Naturopathic Physicians and Integrative Medicine Consortium
    c. McGuff Compounding Pharmacy Services, Inc.

3. FDA Evaluation (**Tab 3c**)

D. Oxitriptan (Tab 4)

1. FDA Evaluation (**Tab 4a**)

III. Neomycin Sulfate - Entry Considered for the Withdrawn or Removed List

A. Neomycin Sulfate (Tab 5)

1. FDA Evaluation (**Tab 5a**)

IV. Points to Consider

A. June 9, 2021, a.m. session

Points for the PCAC to Consider Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulks List

1. FDA is proposing that melatonin for oral administration be INCLUDED on the 503A Bulks List. Should melatonin for oral administration be placed on the list?

2. FDA is proposing that methylcobalamin NOT be included on the 503A Bulks List. Should methylcobalamin be placed on the list?

B. June 9, 2021, p.m. session

Points for the PCAC to Consider Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulks List

3. FDA is proposing that choline chloride NOT be included on the 503A Bulks List. Should choline chloride be placed on the list?

4. FDA is proposing that oxitriptan for oral administration be INCLUDED on the 503A Bulks List. Should oxitriptan for oral administration be placed on the list?

Points for the PCAC to Consider Regarding Whether to Include Certain Entries on the Withdrawn and Removed List

5. FDA is proposing that "Neomycin sulfate: All parenteral drug products containing neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder)" be ADDED to the Withdrawn or Removed List under sections 503A and 503B of the FD&C Act. Do you agree?

Tab 1

Melatonin

Tab 1a

Melatonin Nominations

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
(703) 683-3619 FAX

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Melatonin	acetamide, N-(2-(5-methoxy-1H-indol-3-YL)ethyl)-	Melatonin	JL5DK93RCL	From PCCA MSDS: 100% by weight and stable.		Not USP; sold OTC in US as a dietary supplement.	Capsule Solution Cream Gel Suspension	0.2mg 2mg 3mg 5mg 20mg 0.0125% 0.1% 0.2% 1% 2.5%	Oral Sublingual Injection Ophthalmic		stabilization of sleep cycle

September 20, 2017

Julie Dohm, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

[Docket No. FDA-2015-N-3534]

RE: Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A

Dear Dr. Dohm:

I am writing on behalf of PCCA to formally submit two new nominations to the open docket (ID: FDA-2015-N-3534-0001) for consideration of melatonin and creatine monohydrate to the 503A Bulks List. The patients who rely on these materials to be compounded are primarily those with autism spectrum disorders and mitochondrial disorders affecting muscle, heart and brain function. Please note that the nomination includes safety studies in the bibliography, and while those may be designed for clinical outcomes other than the nominated uses, we included them to assist FDA in your thorough evaluation of the substance. We respectfully ask that this nomination be considered for placement in Category 1 of the 503A Bulks List with urgency. There are no suitable alternative manufactured products for many patients with these serious conditions, and we wish to avoid disruptions in care.

Both melatonin and creatine monohydrate are currently on the 503A Category 3 list. Per FDA's Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, section 3B, "FDA generally expects to categorize bulk drug substances nominated to the October docket and to publish updated categories on its website on the first business day of each month." We understand FDA likely has a detailed internal review process for these types of nominations, and we hope the urgency of the patient need prioritizes this request. We look forward to hearing from you soon.

Sincerely,

Jim Smith
PCCA President

PCCA USA: 9901 S. Wilcrest Drive Houston, Texas 77099 | 800.331.2498 (f) 800.874.5760 | www.pccarx.com
PCCA Canada: 744 Third Street London, ON Canada N5V 5J2 | 800.668.9453 (f) 800.799.4537 | www.pccarx.ca
PCCA Australia: Unit 1, 73 Beauchamp Road Matraville NSW 2036 Australia | 02.9316.1500 (f) 02.9316.7422 | www.pccarx.com.au

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations

Ingredient Name	Melatonin
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	Yes
Chemical Name	N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide
Common Name(s)	Melatonin
UNII Code	JL5DK93RCL
Chemical Grade	NA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	British Pharmacopiea; OTC in US as dietary supplement
Submitted to USP for monograph consideration	Already included in USP Dietary Supplement section
Compounded Dosage Forms	Oral dosage forms as requested by prescriber
Compounded Strengths	0.2 to 20mg
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	1. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. J Pineal Res. 2008;44(1):57-64. 2. Garstang J, Wallis M. Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems. Child Care Health Dev. 2006;32(5):585-9. 3. Wirojanan J, Jacquemont S, et al. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. J Clin Sleep Med. 2009;5(2):145-50. 4. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res. 2012;21:700-9. 5. Malow B, Adkins KW, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. Autism Dev Disord. 2012;42(8):1729-37. doi: 10.1007/s10803-011-1418-3.

6. Giannotti F, Cortesi F, Cerquiglini A, Bernabei P. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. J Autism Dev Disord. 2006;36(6):741-52.
7. Paavonen EJ, Nieminen-von Wendt T, Vanhala R, Aronen ET, von Wendt L. Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. J Child Adolesc Psychopharmacol. 2003;13(1):83-95.

8. Andersen IM, Kaczmarska J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. J Child Neurol. 2008;23(5):482-5. doi: 10.1177/0883073807309783.

9. Gupta R, Hutchins J. Melatonin: a panacea for desperate parents? (hype or truth). Arch Dis Child. 2005;90(9):986-7.

10. Galli-Carminati G, Deriaz N, Bertschy G. Melatonin in treatment of chronic sleep disorders in adults with autism: a retrospective study. Swiss Med Wkly. 2009;139(19-20):293-296.

11. Carr, R., Wasdell, M. B., Hamilton, D., Weiss, M. D., Freeman, R. D., Tai, J., . . . Jan, J. E. (2007). Long-term effectiveness outcome of melatonin therapy in children with treatment-resistant circadian rhythm sleep disorders. Journal of Pineal Research,43(4), 351-359. doi:10.1111/j.1600-079x.2007.00485.

12. Zisapel, N., L., Garfinkel, D., Laudon, M., & N. (2011). Prolonged-release melatonin for insomnia – an open-label long-term study of efficacy, safety, and withdrawal. Therapeutics and Clinical Risk Management,301-311. doi:10.2147/tcrm.s23036

13. Wade, A. G., Ford, I., Crawford, G., Mcconnachie, A., Nir, T., Laudon, M., & Zisapel, N. (2010). Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. BMC Medicine,8(1). doi:10.1186/1741-7015-8-51

14. Russcher, M., Koch, B. C., Nagtegaal, J. E., Ittersum, F. J., Jong, P. C., Hagen, E. C., . . . Wee, P. M. (2013). Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): a randomized controlled trial. British Journal of Clinical Pharmacology,76(5), 668-679. doi:10.1111/bcp.12093

15. Faya, M., Carranza, A., Priotto, M., Graiff, D., Zurbriggen, G., Diaz, J., & Gobello, C. (2011). Long-term melatonin treatment prolongs interestrus, but does not delay puberty, in domestic cats. Theriogenology,75(9), 1750-1754. doi:10.1016/j.theriogenology.2011.01.015

Used Previously to compound drug products	Yes
Proposed use	Adjunctive treatment of autism spectrum disorder
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	

PCCA USA
9901 South Wilcrest Drive
Houston, TX 77099
Tel:281.933.6948

PCCA Canada
744 Third Street
London, ON N5V 5J2
Tel: 800.668.9453

PCCA Australia
Unit 1, 73 Beauchamp Road
Matraville, NSW 2036
Tel: 02.9316.1500

CERTIFICATE OF ANALYSIS

PRODUCT: MELATONIN
ITEM NUMBER: 55-2220
LOT NUMBER: C169246
MFG. DATE: 07/07/2013
EXPIRATION: 07/31/2018

CAS: 73-31-4
MW: 232.2800000000
FORMULA: C13H16N2O2

TEST	SPECIFICATIONS	RESULTS
Ash	<=0.1 %	0.04 %
Assay	98-102 %	99.5 %
Description	pass *WHITE TO OFF-WHITE TO TAN POWDER OR CRYSTALLINE POWDER*	pass *off-white powder*
Heavy Metals	<=10 ppm	10 ppm
Identification	pass	pass
Loss On Drying	<=1.0 %	0.12 %
Melting point	116-120 celsius	119.9 celsius
Purity (HPLC)	>= 99.0 %	99.9 %
Solubility	pass *INSOLUBLE IN GLYCERIN AND WATER; SOLUBLE IN ALCOHOL AND CHLOROFORM*	pass

Bernard Rhee
Tel (direct): 443.519.5540
Fax: 866.941.8799
brhee@tblawadvisors.com

August 2, 2017

Julie Dohm, J.D., Ph.D.
CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

[FDA Docket No. FDA-2015-N-3534]

RE: Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food Drug, and Cosmetic Act; Establishment of a Public Docket

Dear Dr. Dohm:

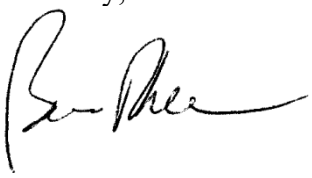
I am writing on behalf of Technology and Business Law Advisors, LLC (TBLA) in reference to FDA's Interim Guidance on Bulk Substances Under Section 503A. Currently melatonin is listed on Category 3: Bulk Drug Substances Nominated Without Adequate Support, and FDA has cited violations by 503A pharmacies for compounding with this substance.

Attached for your consideration is a nomination for it to be placed on FDA's Category 1 list of bulk substances that can be lawfully compounded. Due to the nature of metabolic diseases and the regulatory implications for patient care, TBLA respectfully requests that Melatonin be immediately placed on Category 1 – Bulk Drug Substances Under Evaluation. There are no suitable alternative manufactured products for many patients with sleep disorders, and we wish to avoid disruptions in care.

It is important that compounding pharmacies be able compound melatonin. Although melatonin is widely available as a dietary supplement, it is important that physicians be allowed to prescribe compounded melatonin so that dosage and dosage form can be individualized according to each patient's needs.

Please feel free to contact me if you have any questions about this nomination. Thank you for your prompt consideration of this request.

Sincerely,



Bernard Rhee, Esq.

Encl.

TBLA Submission for Docket No. FDA-2013-N-3534:
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations

Ingredient Name	Melatonin
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	Yes (as a Dietary Supplement)
Chemical Name and Formula	N-[2-(5-methoxy-1H-indol-3-yl)ethyl]acetamide; C13H16N2O2
Common Name(s)	melatonin; melatonine; N-acetyl-5-methoxy tryptamine
UNII Code	JL5DK93RCL
Chemical Grade	USP
Strength, Quality, Stability, and Purity	
How supplied	Powder and other various solid and liquid dosage forms
Recognition in foreign pharmcopeias or registered in other countries	British Pharmacopoeia; OTC in the United States as a dietary supplement
Submitted to USP for monograph consideration	Already included in USP Dietary Supplement section
Compounded Dosage Forms	oral capsules, extended release tablets, immediate release tablets, sublingual tablets, lozenges, oral liquid
Compounded Strengths	1 mg - 1000 mg for solid dosage forms; 1 mg/ml for solution
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	Robert L Sack, Alfred J Lewy & Rod J Hughes (1998) Use of melatonin for sleep and circadian rhythm disorders, Annals of Medicine, 30:1, 115-121, DOI: 10.3109/07853899808999393 Tjon Pian Gi, C.V., Broeren, J.P.A., Starreveld, J.S. et al. Eur J Pediatr (2003) 162: 554. doi:10.1007/s00431-003-1207-x
Used Previously to compound drug products	Yes
Proposed use	General wellbeing and treatment of sleep disorders
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	

Tab 1b

Melatonin
Nomination Clarification

May 11, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA as the nominator of melatonin for inclusion on the 503A Bulk Drug Substances list. Below is our response to FDA's question #1.

1. PCCA does want to pursue review by the FDA and consideration by the PCAC of melatonin for inclusion on the 503A Bulks list. Please note that melatonin does have a monograph in the current USP/NF, and thus meets the statutory requirement for use as an Active Pharmaceutical Ingredient under section 503A of the DQSA.

   The nominated use of compounded melatonin is adjunctive therapy in the management of sleep disorders for patients with autism spectrum disorders. There are no FDA-approved medications for the treatment of insomnia in children and adolescents. Further, medication intolerance and varied dosing protocols require patient-specific compounding of melatonin for patients with autism spectrum disorders.

   Dosing ranges from 0.2 mg to 5 mg orally. In the bibliography below, please note that some of the literature does not study this specific nominated use. Those citations have been included to assist the Agency in your safety review of melatonin.

   a. Gringas P, Tali N, Breddy J, et al. Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry.* 2017 Nov;56(11):948-957.

   b. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res.* 2008;44(1):57-64.

   c. Garstang J, Wallis M. Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems. *Child Care Health Dev.* 2006;32(5):585-9.

d. Wirojanan J, Jacquemont S, et al. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. *J Clin Sleep Med.* 2009;5(2):145-50.

e. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res.* 2012;21:700-9.

f. Malow B, Adkins KW, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *Autism Dev Disord.* 2012;42(8):1729-37. doi: 10.1007/s10803-011-1418-3.

g. Giannotti F, Cortesi F, Cerquiglini A, Bernabei P. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. *J Autism Dev Disord.* 2006;36(6):741-52.

h. Paavonen EJ, Nieminen-von Wendt T, Vanhala R, Aronen ET, von Wendt L. Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. *J Child Adolesc Psychopharmacol.* 2003;13(1):83-95.

i. Andersen IM, Kaczmarska J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *J Child Neurol.* 2008;23(5):482-5. doi: 10.1177/0883073807309783.

j. Gupta R, Hutchins J. Melatonin: a panacea for desperate parents? (hype or truth). *Arch Dis Child.* 2005;90(9):986-7.

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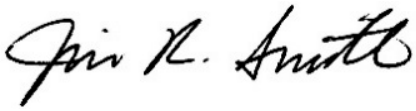
We look forward to providing you further information as requested in the coming weeks.

Sincerely,



Jim Smith
PCCA President

May 25, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA as the nominator of melatonin for inclusion on the 503A Bulk Drug Substances list. The information provided here is not to be considered all-inclusive. Some clinicians may have further information that we were not able to collect by the due date requested.

Below are our responses to FDA's questions #2 and #3:

2. To the best of our abilities, approximately 110,000 prescriptions of compounded melatonin per year are estimated to be dispensed as adjunctive therapy in the management of autism spectrum disorders (ASD).

3. The Autism Research Institute lists melatonin as a highly rated therapy by thousands of parents who responded to ARI's parent surveys. "Its rating of 8.3 to 1 means that for every child in whom a negative effect was noted, more than eight benefited. No sedative, tranquillizer, antipsychotic or anticonvulsant comes anywhere close to such a rating and none of them are as safe as melatonin."[1]

   Natural Medicines Comprehensive Database lists melatonin as "likely effective" in this patient population.[2]

   Autism Speaks has robust information on the role of melatonin in ASD, and has assembled *Melatonin and Sleep Problems in ASD: A Guide for Parents*. As stated on their website, "This tool kit is designed to provide parents with information about melatonin and to help parents decide if trying melatonin is right for their child."

   Several groups under the NHS in the United Kingdom have care guidelines for practitioners regarding melatonin for sleep disorders in children, notably for patients with autism spectrum

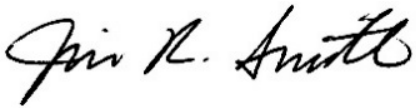
disorders. These guidelines include dosing, safety and patient monitoring information, including indications for use in patients as young as 1-month old.[3-10]

It is important to note that melatonin is not a cure for autism or autism spectrum disorders, or for the sleep dysfunctions that many ASD patients experience. There are no cures for these complex conditions. Melatonin is a valuable tool for clinicians and caregivers when helping to improve the lives of these patients.

There are no FDA-approved products to address sleep dysfunction in patients with ASD.

We hope this information aids the Agency in your review of compounded melatonin. If you require further information, please contact us at your convenience.

Sincerely,



Jim Smith
PCCA President

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2. Melatonin Professional Monograph. https://naturalmedicines.therapeuticresearch.com. Accessed May 24, 2018.
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Tab 1c

FDA Evaluation of Melatonin

DATE: May 7, 2021

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Suhail Kasim, M.D., M.P.H.
Lead Physician, Pharmacy Compounding Review Team (PCRT)
Office of Specialty Medicine (OSM), Office of New Drugs (OND)

Wafa Harrouk, Ph.D.
Senior Pharmacology/Toxicology Reviewer, Division of Pharm-Tox, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine and Office of Specialty Medicine, OND

CDR Oluwaseun (Kemi) Asante, Pharm.D., MPH
Consumer Safety Officer, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Science Advisor (acting), ONDP, OPQ

Daiva Shetty, M.D.
Associate Director, PCRT, OSM, OND

Charles Ganley, M.D.
Director, OSM, OND

Frances Gail Bormel, R.Ph., J.D.
Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Melatonin for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Melatonin[1] is a hormone nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Melatonin was proposed for the treatment of sleep disorders in patients with autism spectrum disorder (specifically children and adolescents) in doses ranging from 0.2 mg - 5 mg for oral administration.[2] The nominator did not propose specific dosage forms to be compounded.[3,4] Because the proposed route of administration is oral, i.e., administration to or by way of the mouth[5], the proposed dosage forms for melatonin could include pill, tablet, capsule, or liquid to be placed in the mouth and swallowed, with absorption taking place in the digestive tract (Verma et al. 2010), and could also include melatonin tablets delivered by the sublingual route (i.e., administration beneath the tongue) or by the buccal route (e.g., lozenge).

Melatonin is marketed in the United States as a dietary supplement. The nominator stated that melatonin has "a monograph in the current USP/NF, and thus meets the statutory requirement for use as an Active Pharmaceutical Ingredient under section 503A of the DQSA" (Drug Quality and Security Act). However, as explained in FDA's 2019 final rule implementing the 503A bulks list (84 FR 4696), FDA does not consider USP monographs for dietary supplements to be "applicable" USP or NF monographs within the meaning of section 503A(b)(1)(A)(i)(I). Although there is a melatonin USP monograph for dietary supplements, there is no official USP or NF drug substance monograph for melatonin; thus, there is no "applicable" USP or NF monograph for melatonin for purposes of section 503A(b)(1)(A)(i)(I).

There are currently no FDA-approved drug products that contain melatonin. However, there are products containing melatonin as an active ingredient licensed and marketed outside the United States for treating sleep disorders in the pediatric and adult population. These products are listed below:

- Circadin 2 mg prolonged-release tablet (Neurim Pharmaceuticals) was approved by the European Medicine Agency (EMA) in 2007 for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients aged 55 years or over (EMA

[1] The common name is melatonin. The CAS (Chemicals Abstract Service, a division of American Chemical Society) name is *N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]acetamide and an additional name for melatonin is *N*-acetyl-5-methoxytryptamine (The Merck Index® *Online*).

[2] Melatonin was also nominated for "stabilization of sleep cycle." However, FDA did not evaluate this proposed use because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for this use in compounded drug products.

[3] On 8/2/2017, Technology & Business Law Advisors (TBLA), LLC nominated melatonin in the compounded dosage forms of "oral capsules, extended release tablets, immediate release tablets, sublingual tablets, lozenges, oral liquid" for the oral route of administration in the compounded strengths of "1 mg - 1000 mg for solid dosage forms; 1 mg/mL for solution" for the proposed uses "general wellbeing and treatment of sleep disorders". Access nomination at: https://www.regulations.gov/document?D=FDA-2015-N-3534-0007

[4] On 9/20/2017, PCCA (Professional Compounding Centers of America) nominated melatonin in "oral dosage forms as requested by prescriber" for the oral route of administration in the compounded strengths of "0.2 to 20 mg" for the proposed use "adjunctive treatment of autism spectrum disorder". Access nomination at: https://www.regulations.gov/document?D=FDA-2015-N-3534-0012

[5] U.S. Food & Drug Administration, Data Standards Manual (monographs), Route of Administration accessed at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071667.htm

assessment of Circadin 2007).[6] Circadin is a melatonin receptor agonist containing melatonin as the active ingredient. It is commercially available in more than 45 countries in Europe, Asia-Pacific, Latin America, Africa and the Middle East (Neurim Pharmaceuticals, Ltd. 2018).

- Slenyto 1 mg and 5 mg prolonged-release minitablets (controlled-release melatonin; Neurim Pharmaceuticals) was approved in 2018 by the EMA Committee for Medicinal Products for Human Use (CHMP) after adopting a positive opinion, for the treatment of insomnia in children and adolescents aged 2-18 with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome (SMS), where sleep hygiene measures have been insufficient[7] Slenyto is a melatonin receptor agonist containing melatonin as the active ingredient (EMA Assessment of Slenyto 2018).
- Melatonin 3 mg immediate-release (film-coated tablet; Pharma Nord) was approved in the UK in 2019 for the short-term (up to 5 days) treatment of jetlag in adults.[8] It was the first licensed indication for a condition other than chronic sleep disorders.
- Melatonin 1 mg/ml oral solution (Colonis Pharma Ltd) was approved in the UK in 2019 for the short-term (up to 5 days) treatment of jetlag in adults.[9]
- Melatobel (melatonin) granules, 0.2%, received marketing approval in Japan in June 2020 for sleep onset difficulty associated with neurodevelopmental disease in children.[10]

There are FDA-approved drug products containing the melatonin receptor agonists ramelteon and tasimelteon, which are tricyclic synthetic analogs of melatonin.[11] [12] Ramelteon drug products are indicated for the treatment of insomnia in adults characterized by difficulty with sleep onset. Tasimelteon capsules are indicated for the treatment of non-24-hour sleep-wake disorder and for the treatment of nighttime sleep disturbances in the genetic disorder SMS in patients 16 years of age and older. Tasimelteon oral suspension is indicated for nighttime sleep disturbances in SMS in pediatric patients 3 years to 15 years of age. Although approved drug products containing ramelteon and tasimelteon may have similar pharmacologic effects to compounded drug products containing melatonin, ramelteon and tasimelteon are structurally different from melatonin and are considered to be different bulk drug substances for purposes of compounding under section 503A.

FDA's evaluation of melatonin's effectiveness was based on information regarding the use of melatonin to treat sleep disorders in children and adolescents with autism spectrum disorder. The discussions of the use of melatonin in the other pediatric populations and in certain adult

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[6] The Circadin summary of product characteristics (prescriber information) can be accessed at http://www.circadin.com/files/17-06-11-ema-UK-SPC.pdf

[7] The Slenyto summary of product characteristics (prescriber information) can be accessed at https://www.ema.europa.eu/en/documents/product-information/slenyto-epar-product-information_en.pdf.

[8] The Melatonin Pharma Nord summary of product characteristics (prescriber information) can be accessed at https://www.medicines.org.uk/emc/product/11018/smpc.

[9] The Melatonin solution summary of product characteristics (prescriber information) can be accessed at https://www.medicines.org.uk/emc/product/10419/smpc.

[10] The company website announcement of Melatobel (melatonin) granules, 0.2% approval can be accessed at https://www.nobelpharma.co.jp/en/research/product/.

[11] See Ramelteon at https://www.accessdata.fda.gov/scripts/cder/daf/. (NDA 021782, ANDA 091610, ANDA 091693, ANDA 211567, ANDA 212650, ANDA 213186, ANDA 213815).

[12] See Tasimelteon at https://www.accessdata.fda.gov/scripts/cder/daf/. (NDA 205677, NDA 214517, ANDA 211607, ANDA 211654).

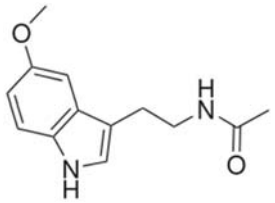
populations are included in the Appendix section of this evaluation as background information. However, the other uses were not considered for the overall assessment and recommendation.

We have evaluated publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of melatonin. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor of*** placing melatonin for oral administration on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).[13]

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding? [14]

Figure 1: Melatonin Structure



Melatonin is a small molecule hormone produced by the pineal gland in animals.

Databases searched for information on melatonin in preparation of this section included PubMed, SciFinder, Analytical Profiles of Drug Substances, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and USP/NF.

1. Stability of the API and likely dosage forms

Melatonin is likely to be stable at room temperature as a solid. Long term stability studies have been performed on one oral formulation of melatonin (capsule 0.5 mg and 6 mg) for up to 18 months at 25 °C / 60 % relative humidity. No trend showing significant degradation of the

[13] Inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required to receive Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on the 503A Bulks List is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

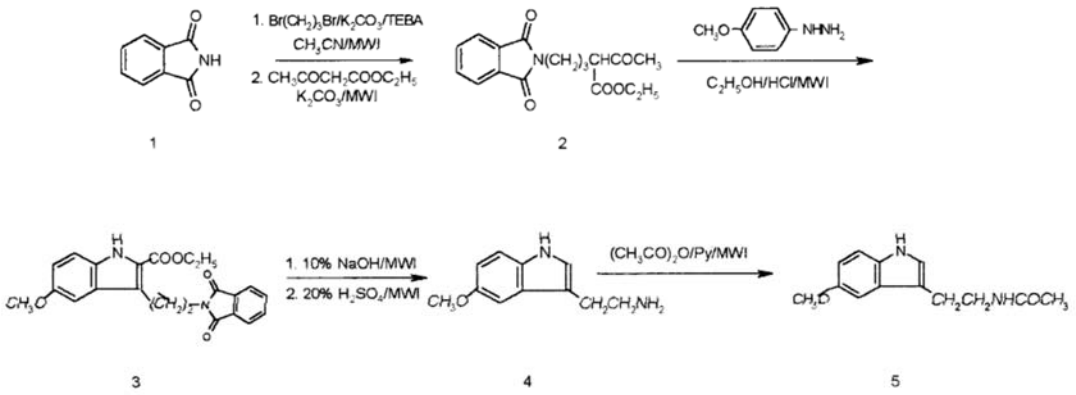
[14] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

API has been observed (Filali et al. 2017). A 0.16 mg/L aqueous solution of melatonin resulted in 22% of the drug substance degradation after 2 weeks at 25 °C when kept away from air. More significant degradation was observed for a similar solution after 6 days in the presence of air (41% after 6 days and 66% after 13 days) (El Moussaoui et al. 2014). However, an aqueous solution of melatonin was observed to be stable for 6 months when stored in sterile vacuum vials at 4 °C (Cavallo and Hassan 1995). In 2019, a 1 mg/ml aqueous oral solution of melatonin was authorized for marketing in UK by Colonis Pharma Ltd as a prescription only drug (authorization number: PL 41344/0050), and a shelf life of 18 months was approved under ordinary storage conditions with protection from light. An in-use period of 2 months is assigned to this product after initial opening of the bottle when the drug product is stored below 25 °C and protected from light. Therefore, melatonin is likely to be stable under ordinary storage conditions in solid dosage forms. With protection from oxygen (air), light and proper formulation components, a relatively stable liquid formulation of the drug substance can be achieved.

2. Probable routes of API synthesis

Multiple synthetic routes have been reported for the manufacturing of melatonin (Szmuszkovicz et al. 1960; He et al. 2003). The following scheme is one example of the chemical synthesis: (He et al. 2003).

Figure 2: Melatonin Chemical Synthesis



Scheme 1.

3. *Likely impurities*[15]

Likely impurities may include:

1) Residual starting materials and reaction intermediates
2) Residual solvents and reagents

4. *Toxicity of those likely impurities*

Per different synthetic routes, some residual reagents and solvents may be toxic. Reagents such as alkyl halides and aldehydes are likely to be involved in the synthesis, which may present structural alert for mutagenicity. Levels of such impurities in the final bulk substance need to be carefully monitored. Further toxicity issues are discussed in Section II.B.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Melatonin is a white to off-white solid, which is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

Melatonin is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Melatonin is a small molecule hormone. It is likely to be stable under ordinary storage conditions as a solid. When compounded as proper liquid formulations (e.g., proper compositions, storage under vacuum or inert atmosphere, protected from light), the product is also likely to be stable. Alternatively, a liquid product can be formulated and stored for a relatively short time under normal atmosphere when protected from light. The expiration period of such a product should be supported by appropriate stability data. The nominated substance is easily characterized with various analytical techniques and the preparation of this substance has been well developed.

[15] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing.

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Embase, Web of Science, ToxNet, NIH dietary supplement label database, Google, GRAS notice inventory, US Pharmacopeia, and Drugs@FDA.

a. General pharmacology of the drug substance

Melatonin is a neurohormone which is almost exclusively synthesized in the pineal gland in mammals. It conveys signals to various organs, principally the brain, which affect the synthesis of second messengers and impacts sleep patterns and circadian rhythms. Using the rat as an experimental model, it was shown that the rates at which the pineal gland synthesizes serotonin and melatonin were associated with circadian rhythms, and that the melatonin rhythm is generated by intrinsic circadian signals originating from the suprachiasmatic nucleus of the brain (Klein and Moore 1979) which are controlled primarily by the light–dark cycle.

Melatonin synthesis starts with the uptake of the amino acid tryptophan from the plasma, followed by 5-hydroxylation (by the enzyme tryptophan hydroxylase), decarboxylation (by the enzyme aromatic L-amino acid decarboxylase) to form 5-hydroxytryptamine or serotonin. During daylight hours, the serotonin in pinealocytes is unavailable to form melatonin (through the action of monoamine oxidase and the melatonin-forming enzymes). During night time conditions, postganglionic sympathetic outflow to the pineal gland increases causing the release of norepinephrine into pinealocytes where stored serotonin becomes accessible for intracellular metabolism. Concurrently, norepinephrine activates the enzymes that convert serotonin to melatonin, allowing melatonin to diffuse out of the pineal gland into the bloodstream and cerebrospinal fluid where plasma melatonin levels rise rapidly (see illustration in Figure 3 below; Wurtman 2005). Due to its high lipid solubility, melatonin diffuses freely across cell membranes into all tissues and is found in the blood largely bound to albumin. Most of the melatonin in the circulation is inactivated in the liver, where it is first oxidized to 6-hydroxy (OH) melatonin by a cytochrome P450-dependent microsomal oxidase and then largely conjugated to 6-sulfatoxymelatonin (6-SMT; the major metabolite of melatonin[16]) or glucuronide before it is excreted in the urine or saliva (Wurtman 2005).

[16] 6-SMT is used to monitor the urinary excretion of melatonin.

Figure 3: Metabolism of Tryptophan to Melatonin in the Pineal Gland

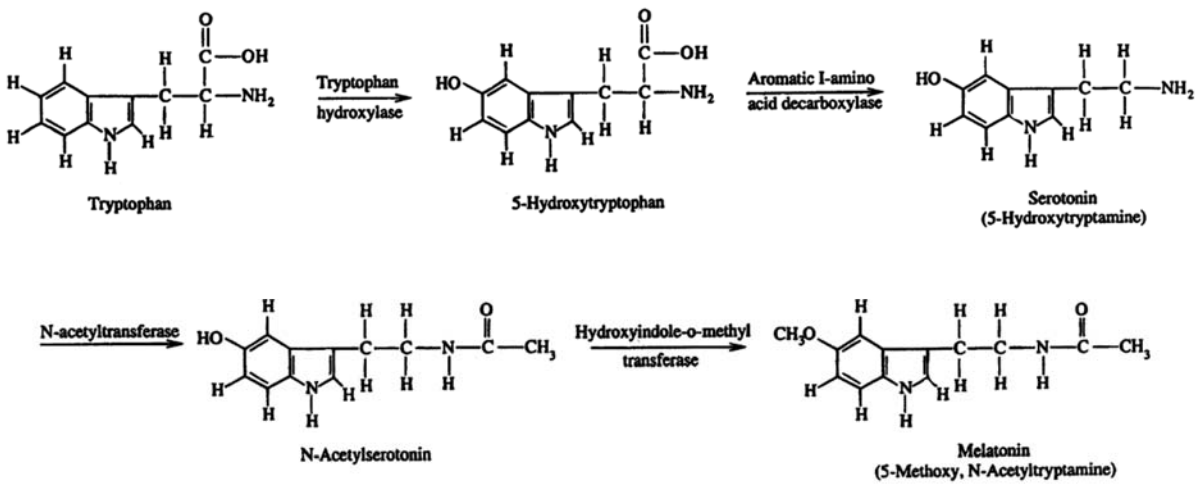


Fig. 1 Metabolism of tryptophan to melatonin in the pineal gland. (Reproduced with permission from Zhdanova, I.V.; Wurtman, R.J. In *Endocrinology: Basic and Clinical Principles*; Conn, P.M., Melmed, S., Eds.; Humana Press, Inc.: Totowa, NJ, 1997; 281.)

The effect of prolonged melatonin administration on several metabolic and hormonal variables was tested in male and female Sprague-Dawley rats (Bojkova et al. 2008). Melatonin was administered in tap water (4 µg/ml) daily to rats (aged 6 months at the start of the study) which were fed standard diet *ad libitum* and were kept in a typical light: dark regimen (12h:12h) for a period of 12 weeks. Throughout the study, female rats showed a decrease in body mass while male rats showed the same effect starting from day 42 of the experiment. Other effects included an increase in the relative heart muscle weight in females and absolute/relative thymus weight in males in the melatonin group. Exposure to melatonin was also associated with decreased glycemia, heart muscle glycogen concentration in females and liver glycogen concentration in both sexes. Serum insulin concentration in males was decreased and serum corticosterone concentration was increased in both males and females. Serum triacylglycerol and heart muscle cholesterol concentrations were decreased in females, whereas serum and heart muscle cholesterol concentration were increased in males. Liver phospholipid concentration was decreased in females and heart muscle phospholipid concentration was increased in males. Melatonin exposure was associated with an increase in malondialdehyde concentrations in heart muscle of treated males and in liver in both sexes. Based on the findings in this study, melatonin seems to induce several sex-dependent changes in both carbohydrate and lipid metabolism pathways. The significance of these biochemical alterations cannot be determined as histology/histopathological assessment was not conducted in this study.

b. Pharmacokinetics/Toxicokinetics

Following a single intravenous injection of melatonin (5 or 15 mg/kg body weight) in propylene glycol in adult male Sprague–Dawley rats, plasma concentrations of melatonin increased to 39 and 199 million pg/mL (0.199 µg/mL) at 2 min, and 128000 and 772000 pg/mL at 120 min, respectively. The initial fall in plasma concentration of melatonin occurred within the first

10–20 min (half-life of 2–3 min) and was followed by a plasma half-life of 20–30 min (See Figure 4 below; Cheung et al. 2006).

Figure 4: Plasma Concentration of Melatonin

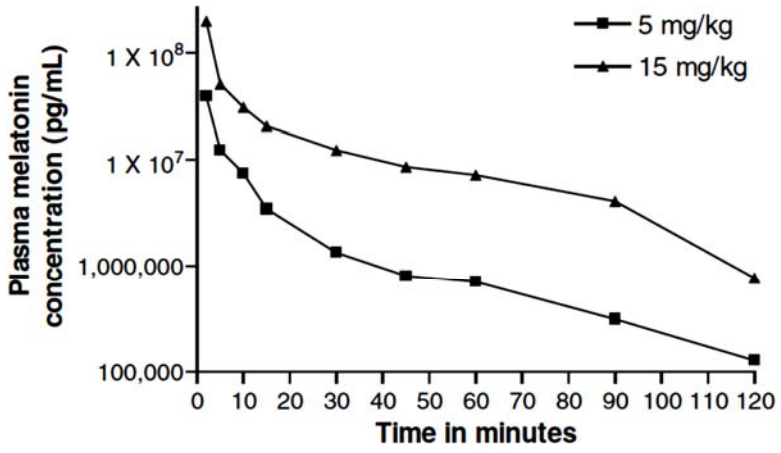


Fig. 1. Plasma concentration of melatonin (in pg/mL) at 2, 5, 10, 15, 30, 45, 60, 90 and 120 min following an intravenous injection at 5 or 15 mg/kg.

A 28-day subcutaneous injection of melatonin in Sprague-Dawley rats showed an increase in melatonin levels at the 3% dose but not in the lower dose of 0.3%. High variability was noted among the groups (See Table 1; Prevo et al. 2000).

Table 1: Serum Melatonin Concentrations (pg/ml)

TABLE 4
Serum melatonin concentrations (pg/ml)

		Males				Females			
Group/treatment		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
I	Mean	ND	ND	ND	BLQ	ND	ND	ND	446.0
Sham-operated	*SD*	—	—	—	—	—	—	—	—
	n	—	—	—	9	—	—	—	1[a]
II/IIS	Mean	141	112	24	58	BLQ	BLQ	BLQ	BLQ
PEG 400	*SD*	38	NA	NA	NA	—	—	—	—
	n	2[a]	1[a]	1[a]	1[a]	3	3	3	10
III/IIIS	Mean	272	527	328	294	340	210	169	257
0.03% melatonin	*SD*	207	222	216	88	78	126	28	170
	n	2	3	3	9	3	3	3	10
IV/IVS	Mean	7990	7313	1803	4222	3020	2480	3058	3113
0.3% melatonin	*SD*	7212	2600	270	1698	546	1723	3501	1724
	n	3	3	3	10	3	3	3	10
V/VS	Mean	2167	40933	44500	33644	21300	19733	22567	52678
3.0% melatonin	*SD*	15252	17074	9215	24498	9443	13966	8113	24760
	n	3	3	3	10	3	3	3	9

Notes. ND = not determined: NA = not applicable; BLQ = below level of quantitation.
[a]One or more samples were BLQ and not included in the calculations.

Sleep induction was observed in all rats administered intranasal melatonin formulation (melatonin niosomes) within 15 min of dosing. Intranasal delivery of melatonin in rats showed delayed absorption, lower exposure (AUC), faster clearance (CL), longer exposure ($t_{1/2}$) when compared with melatonin injected via the intravenous route (See Table 2; Priprem et al. 2017).

Table 2: Pharmacokinetic Parameters of Intranasal Melatonin-Encapsulated Niosomes and Intravenous Melatonin Solution in a Crossover Design Studies in Rats (n = 8 each)

Table 2. Pharmacokinetic parameters of intranasal melatonin-encapsulated niosomes and intravenous melatonin solution in a crossover design studies in rats (n = 8 each).

Parameters	Intranasal melatonin niosomes (0.02 mg/rat)	Intravenous melatonin injection (0.02 mg/rat)
CL (ml/h/kg)	1602 ± 612	1189 ± 579
Vd (ml)	2.2 ± 0.6	2.1 ± 1.6
Vz (ml)	7.7 ± 0.8	1.9 ± 0.9
C_{max} (ng/ml)	12.6 ± 6.1	33.0 ± 6.8
Half-life (min)	123.1 ± 81.9	71.5 ± 53.3
T_{max} (min)	18.3 ± 7.5	Not determined
MRT (min)	159.2 ± 110	96.0 ± 51.4
AUC (ng min/ml)	1189 ± 579	1601 ± 612
Bioavailability (%)	98.7 ± 23.6	100

CL: Clearance; C_{max}: Maximum concentration; MRT: Mean residence time (AUC_{tot}/AUC_{tot}); T_{max}: Time to reach the maximum concentration; Vd: Volume of distribution (at steady state); Vz = During terminal phase.

Administration of melatonin solution (0.5, 3, 5 and 10 mg) in a liquid food formulation to baboons (n=3) for 3 consecutive day, twice daily (morning and evening) showed a decrease in the evening's activity among animals dosed with 5 and 10 mg melatonin but did not affect the circadian rhythm of dosed animals. Dosing of melatonin (0.5 mg) was associated with an increase in melatonin levels when measured 1hr after dosing in 2 baboons (108 and 168 pg/mL) as compared to control animals (1.5 and 1.3 pg/mL) (Hao and Rivkees 2000).

c. Acute toxicity[17]

Acute toxicity studies for melatonin conducted in the mouse and rat models using different routes of administration exhibited low toxicity profile for melatonin as shown by the high doses required to reach LD_{50} values (see Table 3; Sugden et al. 1983).

Table 3: Acute Toxicity of Melatonin – LD_{50} Values

TABLE 1

Acute toxicity of melatonin

This table compares the LD_{50} values of melatonin by different routes of administration in the mouse and rat. The numbers in parenthesis indicate the 95% confidence limits of each LD_{50} value. Five mice or three rats were used at a minimum of four to five dose levels.

Route of Administration	LD_{50} (mg/kg)	
	Mouse	Rat
i.p.	1168 (987–1382)	1131 (800–1600)
oral	1250 (1090–1434)	>3200
s.c.	≫1600	≫1600
i.v.	472 (400–564)	356 (115–1105)

Single intravenous doses of melatonin (5 or 15 mg/kg) diluted in 10% propylene glycol did not show any major toxicities in the rat; changes were limited to alterations in the level of some metabolic enzymes at 60 min after injection (increased levels of creatine, aspartate transaminase and lactate dehydrogenase) when compared to levels measured prior to melatonin injection. Within 60 min of injection, blood pressure, heart rate and body temperature of treated rats remained unaffected. Gross pathological examination of the brain, kidney, liver and spleen did not reveal any evidence of toxicity. In addition, six daily injections of melatonin (intravenous injection in propylene glycol) did not show any gross or histopathological changes. The only change observed was a 5.5% reduction in body weight 24 hours after the injection, which may have been a transient change or associated with the use of vehicle, propylene glycol.[18] In the absence of a reversibility arm in the study, it is not possible to associate the effect of melatonin exposure on body weight changes (Cheung et al. 2006).

[17] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[18] See https://www.ema.europa.eu/documents/report/propylene-glycol-used-excipient-report-published-support-questions-answers-propylene-glycol-used_en.pdf.

d. Repeat dose toxicity[19]

A 28-day toxicity study was conducted in Sprague-Dawley rats (n=19/sex/group) where melatonin was delivered continuously via a subcutaneously implanted osmotic pump (60 μl/day of vehicle (polyethylene glycol 400), 0.03%, 0.3%, or 3% melatonin). The calculated dose of melatonin delivered based on weekly group mean body weights was approximately 0.050, 0.50, and 4.8 mg/kg/day for the male groups and 0.074, 0.75, and 7.3 mg/kg/day for the female groups, respectively (n = 10). An additional sham-operated group (n=19/sex) was included in the study. No deaths or abnormal clinical observations occurred that were attributed to melatonin. No drug related effect was seen in body weights, hematology, clinical chemistry, urinalysis, or gross pathology. A dose-related trend of increased serum melatonin concentrations occurred in males and females. In males, there was a trend towards a decrease in serum prolactin concentrations in all melatonin-treated animals. No difference in serum follicle-stimulating hormone concentrations was noted in melatonin-treated groups when compared to control cohorts. A dose-related increase in urine 6-SMT (the primary metabolite of melatonin) concentrations occurred in melatonin-treated rats of both sexes. No treatment-related organ weight or histopathological changes were noted in rats infused with 0.03% or 0.3% melatonin. In two male rats (out of 10 males) administered 3.0% melatonin, a decrease in testicular weights along with testicular degenerative changes (reduced or absent spermatogenesis, spermatidic giant cells, and edema) were seen at the end of the study (Prevo et al. 2000).

A 90-day toxicity study compared the toxicity profile of intranasally vs. intravenously administered melatonin (Priprem et al. 2017). Acute (single dose, 0.2 mg) and subchronic (90-day, 0.2 mg) exposure to melatonin did not impact clinical signs, behavior or hematological profiles in treated animals. Transient nasal irritation with no signs of inflammation was observed in rats treated with intranasal melatonin, indicating the nose is a potentially safe and feasible route of administration for melatonin.

A 90-day oral gavage toxicity of melatonin in rats (0.3, 1.2 and 6 mg/kg/day) showed minimal toxicities which were limited to a decrease in body weight gain among mid (males) and high doses (males and females) treated animals. Decreased testis and increased kidney relative weights were also observed at the 6 mg/kg dose (EMA assessment of Circadin 2007).

A 90-day oral gavage toxicity study of melatonin in male and female Long-Evans rats (0, 5, 50, 5,000, 50,000, and 200,000 µg/kg) did not impact survival, terminal body weights or organ weights of treated rats. In the same report, Fischer 344 rats (males and females) were dosed by gavage treatment with 0, 5, 50, 5,000, 50,000, and 200,000 µg/kg of melatonin for 13 weeks. While the study showed no effects on survival or organ weights, terminal body weights were decreased by 5, 9, and 11%, in the 5,000, 50,000, and 200,000 µg/kg treated males, respectively. These decreased terminal body weights were statistically significant and appear to be related to melatonin administration. No gross pathology findings, neoplastic or nonneoplastic microscopic findings were interpreted to be treatment related (Gerken et al. 2003, cited in Scientific Committee on Consumer Safety report on melatonin, 2010).

[19] *Repeated-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

A 13-week and a 26-week oral rat toxicity study of melatonin (15, 75, and 150 mg/kg) showed limited toxicities. At the 13-week time point, changes included increased hemoglobin concentrations and platelet counts at 75 and 150 mg/kg/day among treated animals. Increased liver weights with minor centrilobular hepatocytic hypertrophy were also observed. Increased testes, prostate and epididymal weights were seen in mid and high dose treated males. At the 26-week time point, macroscopically dark thyroid was noted in high dose animals. At the microscopical level, changes were limited to minor liver hypertrophy which was seen in some high dose animals, a finding which was reported to be more pronounced in the 13-week toxicity study (EMA assessment of Circadin 2007).

A 6-month oral toxicity study conducted in dogs, exposure to melatonin (0.4, 1.5, and 8 mg/kg) showed toxicities which were limited to treatment-related increases in serum glucose levels. However, the changes were variable and were not dose-related and thus were not considered to be toxicologically-relevant findings. Microscopic examination of melatonin-treated dogs revealed pituitary gland and parathyroid cysts, adenomyosis of the uterus, capsular fibrosiderosis of the spleen and cytoplasmic rarefaction of hepatocytes consistent with the presence of glycogen. The summary was provided in the EMA assessment of Circadin (2007) and did not provide detailed information on whether these findings were also observed in control cohorts.

Juvenile Toxicity

Melatonin was tested for toxicity in juvenile animals as reported in the EMA report of Circadian (2007) as well as in the approval package for melatonin prolonged-release minitablets (Slenyto; approved on July 26, 2018) which is indicated for treating insomnia in 2 to 17-year-old children and adolescents with autism spectrum disorder, in addition to approval for use in patients with SMS) (EMA Assessment of Slenyto 2018). A 14-day rat juvenile toxicity study was conducted to determine the maximum tolerated dose (MTD) of melatonin and to define dose levels for the subsequent pivotal juvenile toxicity study. No mortality or morbidity was observed during the treatment. No melatonin-related effects were observed for any of the in-life parameters, organ weight or macroscopic findings. The pivotal study was a 70-day repeat-dose toxicity study, which was conducted to determine the systemic toxicological and toxicokinetic profile of melatonin following daily oral administration (20, 80, 160 mg/kg/day) to juvenile male and female rats and to evaluate the reversibility of any effects observed following a 14-day recovery period. No mortality or morbidity was observed during the treatment period. No melatonin-related effects on clinical signs, body weight, food consumption, ophthalmology, estrous cyclicity, sexual maturity, sperm parameters or macroscopic changes were observed. Significantly higher percentage of abnormal sperms were observed in all treated male dose groups (up to 5% at the low and mid doses and up to 9% at the high dose); however, these findings were found to be within the historical control for this strain of rats (which was noted to be up to 21.5%). In the same study, no adverse effects were noted for the central nervous system (functional observation battery), endocrine/reproductive systems (estrous cyclicity, vaginal opening, preputial separation, and sperm quality) up to ≥80 mg melatonin/kg/day by the oral route. Toxicokinetic data from the 70-day juvenile toxicity study showed that AUC_{last} increased with dose in a greater than dose proportional manner between 20 and 80 mg/kg, but in a dose-proportional manner between 80 and 160 mg/kg. No notable gender differences were observed. Compared to the exposure of melatonin in adult rats, melatonin exposure in juvenile rats was

higher at similar dose levels, but the NOAEL (no observed adverse event (AE) level) in both age groups was observed at similar dose levels of melatonin.

e. Genotoxicity[20]

A standard battery of genotoxicity tests has been performed for melatonin. The Ames test, *in vitro* gene mutations in mouse lymphoma cells, *in vitro* chromosome aberration in human lymphocytes and *in vivo* mouse micronucleus were all negative (EMA assessment of Circadin 2007).

Other studies have shown that both melatonin and its main metabolite, 6-hydroxymelatonin, were not mutagenic in an Ames test using three strains of *Salmonella typhimurium* (Neville et al. 1989).

f. Developmental and reproductive toxicity[21]

Rat

Adverse effects were noted in a 28-day toxicity study where 2 out of 10 male rats subcutaneously administered a dose of 3.0% melatonin showed a decrease in testicular weights along with some testicular degenerative changes including reduced/absent spermatogenesis, spermatidic giant cells and edema (Prevo et al. 2000).

A study assessing the fertility and early embryonic development effects of melatonin was conducted in rats (n= 25 animals/sex/dose) dosed orally by gavage with 0, 50, 100 or 200 mg/kg/day melatonin. The estrous cycle, mating performance, and male fertility parameters (sperm number, motility and morphology) were unaffected by the treatment. Although not statistically significant, abnormal effects included an increase in the mean incidence of preimplantation loss in the high dose group (15%) when compared to concurrent controls (7.5%); which was slightly higher than the incidence in background control range of the National Toxicology Program (NTP) database (8.7% to 14.5%). No effects on post-implantation loss was seen among treated animals (Jahnke et al. 1999).

Melatonin was orally administered by gavage to pregnant rats (n=25) from gestation day (GD) 6 to 19 at doses of 50, 100, and 200 mg/kg/day. No maternal deaths were observed, and some minor clinical signs were seen. Transient reduction of the body weight gain and relative decrease in food intake were observed at the high dose group. Increased relative maternal liver weight was also observed among mid and high dose treated animals. Absolute liver and gravid uterine weights were not affected.

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[20] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

[21] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

Melatonin was orally administered to pregnant rats (n=24) from GD 6 to post-natal day (PPD) 21 at doses of 0 (control), 15, 55 and 200 mg/kg/day. No effect was noted on parturition or outcome of pregnancy. Some effect on growth and viability of the high dose offspring was seen during the postnatal (lactation) stage of development. At weaning, a slight reduction of offspring growth was observed in all dose groups, but no effects were seen in subsequent F1 generation (EMA assessment for Circadin 2007).

Rabbit

Melatonin was orally administered by gavage to pregnant New Zealand White rabbit from GD 7 to 19 at 0 (control), 15, 50 and 150 mg/kg/day. No dose-related maternal effects were seen at any dose level. No effects were observed on pre- or post-implantation loss or mean number of fetuses/dam. Fetal, litter and placental weighs were not affected by treatment. Visceral and skeletal malformations and/or variations were observed in all groups including controls. Some malformations/variations showed a trend or a significant increase in the treated groups, such as absence of lung or iliac alignment/caudal shift of vertebrae in the high dose group (EMA assessment for Circadin 2007).

g. Carcinogenicity[22]

A short-term carcinogenicity study was conducted in transgenic mice (hemizygous TG.NK female mice with MMTV/c-neu oncogene[23]) to study the impact of melatonin (50-200 mg/kg) alone or with flaxseed oil (melatonin 50 mg/kg combined with 0.10ml flaxseed oil) on the incidence of breast tumor occurrence and regression (Rao et al. 2000). When dosed alone, melatonin showed a trend towards delaying the occurrence of mammary tumors and was associated with a decrease in the number of tumors (per mouse) among mice dosed with 50 mg/kg melatonin but no changes were noted at the 100 mg/kg dose (see Table 4 below, from Rao et al. 2000).

[22] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

[23] MMTV/c-neu is the human breast cancer oncogene homologue of *erb*B2.

Table 4: Body Weigths, Number of Mammary Tumors, Mammary Tumor Weigths and IGF-1 Concentrations of TG NK Mice Gavaged with Melatonin and/or Flaxseed Oil

Table 3. Body weights, number of mammary tumors, mammary tumor weights, liver weights and IGF-1 concentrations of TG.NK mice gavaged with melatonin and/or flaxseed oil

Treatment	Number of mice	Body weight (g)[1]	Incidence (%)	No. of tumors per mouse[2]	Multiplicity[3]	Weight (g) of tumors/mouse[4]	Mean tumor weight (g)[3]	Liver weight (g)	IGF-1 ng/ml
Control (NTP-2000 + 0.2 ml Corn oil)	12	24.3 ± 0.76[5]	83.3	1.75 (21/12)	2.10 ± 0.28	0.53 ± 0.15	0.64 ± 0.16	1.13 ± 0.05	308.7 ± 19.6
Melatonin 50 mg/kg	13	23.9 ± 0.57	38.5*	0.69 (9/13)*	1.80 ± 0.49	0.08 ± 0.05*	0.21 ± 0.11*	1.09 ± 0.04	310.9 ± 15.9
Melatonin 100 mg/kg	11	22.8 ± 0.37	81.8	1.18 (13/11)	1.44 ± 0.24	0.23 ± 0.09*	0.28 ± 0.10*	1.03 ± 0.03	305.6 ± 13.9
Melatonin 200 mg/kg	8	22.5 ± 0.31	25.0*	0.25 (2/8)*	1.00 ± 0.00*	0.16 ± 0.16*	0.63 ± 0.62	1.02 ± 0.02	278.7 ± 17.5
Flaxseed oil 0.05 ml/mouse	12	24.1 ± 0.55	100	2.25 (27/12)	2.25 ± 0.33	1.08 ± 0.40	1.08 ± 0.40	1.14 ± 0.03	284.9 ± 21.4
Flaxseed oil 0.10 ml/mouse	11	23.0 ± 0.47	81.8	1.45 (16/11)	1.78 ± 0.36	1.20 ± 0.56	1.47 ± 0.66	1.11 ± 0.05	341.3 ± 15.6
Flaxseed oil 0.20 ml/mouse	10	23.9 ± 0.57	70.0	1.00 (10/10)[6]	1.43 ± 0.20	0.25 ± 0.14*	0.36 ± 0.19*	1.10 ± 0.03	323.4 ± 19.8
Flaxseed oil + Melatonin (0.10 ml + 100 mg/kg)	14	22.8 ± 0.29	64.3	1.00 (14/14)*	1.56 ± 0.24	0.24 ± 0.11*	0.38 ± 0.15*	1.08 ± 0.03	270.3 ± 11.5*

[1]Body weight in grams after 20 weeks on study (24 weeks of age), before tumor development.
[2]Average for all mice in the group including the mice with no tumors (total number of all tumors/number of mice in the group).
[3]Average for only the mice with tumors.
[4]Average for all mice in the group including the mice with no tumors (total weight of all tumors/number of mice in the group).
[5]Mean ± Standard error.
[6]$p < 0.06$.
*$p < 0.05$.

In a combined rat chronic toxicity and carcinogenicity study (104-week study), an increased incidence of pituitary adenomas was seen in high dose treated males (statistical significance at $p<0.036$). In addition, thyroid tumors were observed at the higher doses in rats. Liver enzyme induction was suggested as the possible mechanism of the tumor incidence (no supportive data had been cited). An increased incidence of thyroid macroscopic and microscopic findings was apparent in treated animals when compared to their counterpart controls; however, the thyroid findings were not clearly correlated with the liver findings (see Table 5; EMA assessment of Circadin 2007).

Table 5: Incidence of Thyroid Neoplastic and Non-neoplastic Lesions in the 104 Rat Carcinocenicity

Table: Incidence of thyroid neoplastic and non-neoplastic lesions in the 104 rat carcinogenicity

	Male		Female	
	Neoplastic[a]	Non-neoplastic[b]	Neoplastic[a]	Non-neoplastic[b]
Control	15/100 (15.0%)	10/100 (10%)	11/99 (11.1%)	2/99 (2%)
15 mg/kr	5/17 (29.4%)	3/17 (17.6%)	5/22 (22.7%)	0/22 (0%)
75 mg/kg	8/29 (27.6%)	12/29 (41.4%)	2/29 (6.9%)	13/29 (44.8%)
150 mg.kg	13/50 (26.0%)	21/50 (42%)	4/50 (8.0%)	14/50 (28%)

[a] B-C-cell adenomas + all thyroid carcinomas

[b] B-follicular cell hypertrophy

Conclusions: Acute animal toxicity studies show a high threshold of toxicity for melatonin. Exposure to melatonin (at doses up to 3% subcutaneously) for up to 28 days was not associated with adverse effects except for some testicular effects. Melatonin did not have genotoxic adverse effects. Developmental studies in the rat did not show embryofetal toxicities. Some malformations were noted in the rabbit when dams were dosed at 150 mg/kg/day. The carcinogenic potential of melatonin in the rat showed an increased incidence of pituitary adenomas and thyroid tumors among animals treated with 150 mg/kg/day when compared to control vehicles. Melatonin exposure was associated with a delay in the incidence of tumor progression in one form of breast cancer in a transgenic mouse model.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), and ClinicalTrials.gov.[24]

a. Reported adverse reactions (FAERS, CAERS)

FAERS

The Office of Surveillance and Epidemiology (OSE) conducted a search of the FAERS database, the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS), in addition to a review of the medical literature for reports of AEs and potential safety signals for melatonin from January 1, 2008 through December 31, 2020.

FAERS report executive summary

- For the identified AEs and case reports in the OSE analysis, the AEs were either consistent with the known safety profile of melatonin including information discussed in the literature, or confounded by concomitant medication/disease state, or lacked enough details precluding

[24] Per search of ClinicalTrials.gov conducted on 03/07/21, 534 studies listed melatonin as an intervention.

the ability to determine a drug-event association. The AEs also primarily consisted of acute reactions to exposure rather than exposure data for longer-term effects.

- ***None of the cases reported included information regarding the use of a compounded melatonin product***. There was no information about the exact contents of any melatonin products reported in these cases and cannot be confirmed.
- There was an upward trend in reported FAERS AE cases and in the AAPCC NPDS data for overall exposures reported with melatonin use, especially for the reports of childhood melatonin exposures.
- General unintentional exposure (82.3%, 153297/186282) and therapeutic error (9.1%, 17032/186282) were the most common reported reasons for all calls recorded in AAPCC NPDS. Overall, the calls related to general unintentional exposure comprised of younger children, with 91.4% (140110/153297) being reported in children under the age of five years.
- There was insufficient information regarding the safety of long-term melatonin use, particularly in children.

Summary discussion of FAERS database findings and the literature reports

- No cases involved a compounded melatonin product.
- For the serious events identified, in the 7 to <17 year-old age group there were five reports, in the 17 to <65 year-old age group there were 23 reports and in individuals ≥65 year-old there were 21 reports.
- One death was reported in the FAERS database although the event was confounded by the patient's underlying health condition.
  - *FAERS case #15935767*
    Preferred terms: Drug interaction; General physical health deterioration; Hallucination; Lung squamous cell carcinoma metastatic
    The case describes an 81-year-old female with lung squamous cell carcinoma and Parkinson's disease who was taking pimavanserin for hallucinations and delusions associated with Parkinson's disease psychosis, diphenhydramine for an unknown indication, and melatonin for an unknown indication. Her son reported a possible drug-drug interaction with melatonin and diphenhydramine leading to an increase and worsening of the patient's hallucinations. The patient later died due to metastatic squamous cell carcinoma of the lung. No further information was provided.
- One infant death was reported in the literature. The parents, who reportedly had no medical training and had not acted under a physician's guidance, had been regularly administering up to 40-50 mg of dissolvable melatonin daily for an unspecified period, apparently as a sleep aid. The infant twin was found unresponsive next to her surviving twin. The post-mortem examination revealed a melatonin blood level of 1400 ng/mL (reporting limit = 100 ng/mL), which was "well above the expected endogenous levels in both pediatric and adult patients."
- Cases described a wide range of dosing from 1 mg to ≥ 10 mg daily.
  - In the cases that reported time to onset, the majority (72.7% (16/22)) reported the AE occurring within 1 week or less, indicating that most AEs were a result of short-term use of the product rather than longer term effects after chronic use.
- Majority of reported AEs (71%, 42/59) were confounded by concomitant drug, disease state, or both.

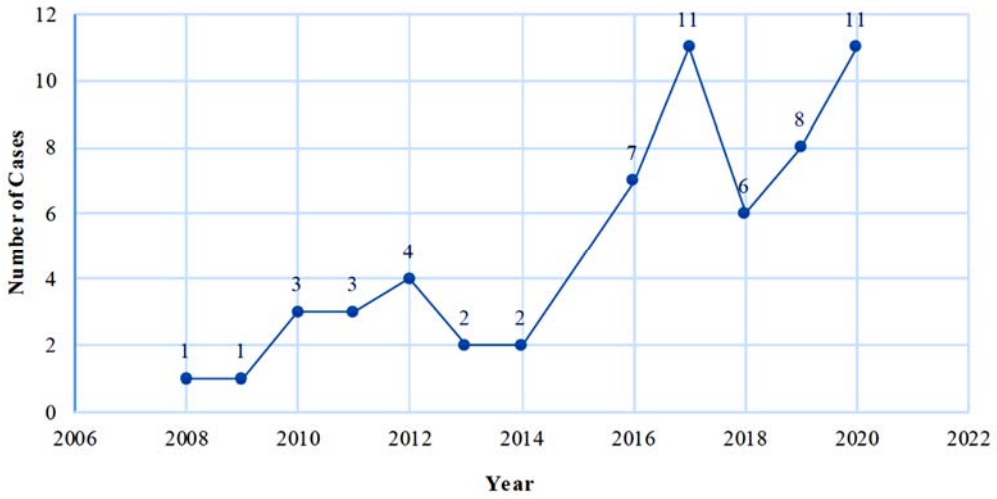
- Adverse events were reported in six cases that involved single-substance melatonin. These AEs included parasomnia (nightmares), altered mental status ("odd feeling in my head"), weakness due to possible myasthenia gravis flare, sharp heart pain, and two events of feeling groggy.
- Many of the most frequently reported preferred terms for the AEs included hallucination, somnolence, dizziness, insomnia, nightmare, etc. that are expected considering melatonin's known mechanism of action and use (i.e., to induce sleep).

- Three patients reported use for sleep disorder in autism spectrum disorder or neurodevelopmental disorder:
  - 16-year-old male with Asperger's syndrome using melatonin to treat insomnia from the use of Concerta (dose, duration not reported) experienced restlessness, mild dysphoria, hallucinations, lightheadedness, and insomnia after taking 3 mg melatonin once daily for one day. Melatonin was discontinued, and the AEs resolved (positive dechallenge). Action with Concerta was not reported.
  - 8-year-old female with attention-deficit/hyperactivity disorder (ADHD), neurodevelopmental disorder, and sleep disorder received melatonin 5 mg daily at bedtime for one year. She was reported to have "recently" switched from Vyvanse to Concerta. She experienced irritability and agitation one month after an increase in dose of Concerta. Concerta dose was decreased and patient experienced difficulty falling asleep, hallucinations, and suicidal thoughts. Concerta was discontinued, and melatonin was continued. The outcome was not reported.
  - 10-year-old male with autism was on melatonin 3 mg daily at bedtime for 3-4 years. He had a 2-year history of abdominal pain, heartburn, dysphagia, and an endoscopy revealed eosinophilic esophagitis. He also experienced muscle aches. The outcome was not reported.

    All three cases highlighted the medical complexities, including polypharmacy, of children/adolescents with autism spectrum disorder or neurodevelopmental disorders. One case described melatonin being used to treat another medication side effect (Concerta's insomnia). Missing information (outcome in 2 cases) and confounding factors make these cases difficult to assess. Two cases were confounded by Concerta (labeled for psychiatric adverse events in Section 5.2 WARNINGS AND PRECAUTIONS; insomnia and anxiety in ADVERSE REACTIONS section).

Figure 5 below copied from the OSE analysis display the trend for 59 unique cases of serious adverse events (SAE) (Male=22; Female=33; unknown=4) with melatonin use that were included in the cumulative FAERS cases series report from January 1, 2008 through December 31, 2020. Although the numbers were small, overall, there was an increasing trend over time of SAE cases with melatonin reported to FAERS. Similar trend was observed with rising numbers of reports to the AAPCC NPDS (See Figure 6 below). The trend may be secondary to the increased use of melatonin (Grigg-Damberger and Ianakieva 2017).

Figure 5: Trend of Serious Adverse Event Cases with Melatonin Included in the Cumulative FAERS Case Series from January 2008 –December 2020 (N=59)

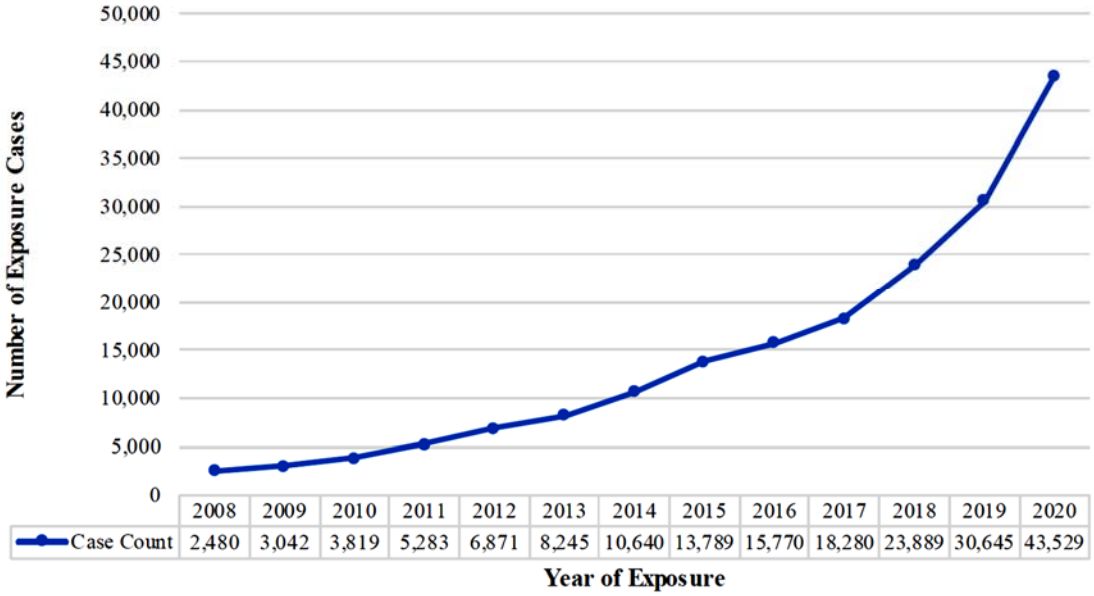


Source: OSE FAERS report for melatonin (2018-1754)

Summary discussion of the AAPCC NPDS database

- Similar to the trends in Figure 5 of the FAERS reports, Figure **6** below displays the number of melatonin-involved exposure cases documented by U.S. poison control centers per year that included a summary of aggregate counts per year with single substance exposure to melatonin, meaning exposure to a single product containing melatonin alone. The figure demonstrates a steady increase in reports over the past seven years.
- General unintentional exposure (82.3%, 153297/186282) and therapeutic error (9.1%, 17032/186282) were the most commonly reported reasons for all calls to U.S. poison control centers.
- Overall, poison control center calls related to general unintentional exposure were predominately comprised of younger children, with 91.4% (140110/153297) being reported in children under the age of five years.
- The most frequently reported and documented clinical effect by U.S. poison control centers was drowsiness/lethargy (58.5%, 16920/28930), which is a known and expected AE associated with melatonin use given its mechanism of action and use (i.e., sleep disorders). Although less commonly reported, the remaining top ten related clinical effects, which include CNS depression, nausea/vomiting, agitation, abdominal pain, dizziness/vertigo, tachycardia, and headache, are all known AE that have been described with melatonin use.

Figure 6: Melatonin-Involved Single Substance Exposure Cases Documented by U.S. Poison Control Centers Per Year, January 1, 2008 –December 31, 2020 (N=186,282)



Source: OSE FAERS report for melatonin (2018-1754)

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of AE involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted in August 2020 for AEs associated with melatonin based on the term "melatonin." A total of 238 CAERS cases were spontaneously reported from July 2007 through August 2020 that included at least one AE in association with the use of melatonin. Some cases listed as many as 73 different ingredients in the suspect product containing melatonin and many of the CAERS melatonin cases were confounded by either other ingredients in the suspect melatonin product or melatonin was used with other concomitant medications.[25] Few case reports listed melatonin as the only active ingredient in the suspect product and the use of concomitant products was not reported.

The following CAERS cases provide examples of the wide range of AEs reported in the relatively few case reports that listed melatonin as the only active ingredient.

- *Report ID #142574*
  20-year-old female with no reported medical history of other illnesses or history of food allergies consumed one melatonin 300 mcg tablet and developed hypersensitivity reactions characterized by dyspnea, tachycardia, generalized rash and ocular hyperemia. She obtained medical care, and the adverse reactions resolved after discontinuing the product.

[25] It was difficult to accurately determine the total number of melatonin CAERS cases confounded by concomitant medications because even when the concomitant medications field was blank, the use of concomitant medications was frequently mentioned in the narrative field.

- *Report ID #145127*
  59-year-old female with significant medical history of other illnesses and history of food allergies consumed one melatonin 300 mcg tablet and developed hypersensitivity reactions characterized by oropharyngeal swelling with throat tightening, dysphonia, and generalized urticaria. She self-treated with diphenhydramine 50 mg orally and administered an epi-pen to herself. There was no additional information available.
- *Report ID #148686*
  37-year-old male consumed one melatonin 3 mg tablet and developed anxiety, muscle spasm and body pain for which he was hospitalized for back injury with hypokalemia, dystonia, muscle spasms, and pain. He was managed with anxiolytics and discharged on citalopram. There was no additional information available.
- *Report ID #151616*
  Subject consumed melatonin 10 mg as sleep aid for two weeks and was hospitalized (life-threatening) after developing dependence, aggression, anorexia, insomnia, mental status and behavioral changes with somnambulism. The subject stated, "I totaled my car, ran through the woods naked, went completely insane, screaming and fighting the emergency people that were trying to help me." The melatonin level was 73.0 pg/ml.
- *Report ID #154079*
  An adult female with no prior history of seizures who used melatonin 5 mg tablets regularly as sleep aid for four years reported to her doctor regarding experiencing an episode of convulsion (became incoherent, could not speak, and shook violently) after discontinuing melatonin for five days. There was no additional information available.
- *Report ID #157061*
  10-year-old boy with no prior history of seizures or other ongoing medical illness used melatonin 3 mg tablets at bedtime as sleep aid for two weeks. He developed convulsions at school with eye rolling, hallucination, skin discoloration and was then observed in the emergency room (CT scan negative; no abnormal labs reported). Following melatonin discontinuation, the boy began experiencing hallucinations, and was to be followed by neurologist. There was no other information reported.
- *Report ID #182089*
  48-year-old female who used melatonin 3 mg to aid in sleep intermittently up to four times developed hypopnea, insomnia, and palpitations after taking the last dose. The symptoms resolved after treatment discontinuation.
- *Report ID #186758*
  67-year-old female with cardiovascular comorbidities of hypercholesterolemia and hypertension used melatonin 10 mg capsules for five years. She was hospitalized after experiencing cerebrovascular accident (stroke) and fall.
- *Report ID #188491*
  65-year-old female with history of breast cancer on multiple antihypertensives was using melatonin dietary supplement pro-advanced formula 220 (2 capsules/daily orally) for between one to two months when she developed elevated liver enzyme and weight loss. There was no other information reported regarding clinical course.

Regarding the outcomes listed for the 238 CAERS cases that included melatonin use, 142 cases reported information for at least one medically important event, 81 cases reported hospitalization and 14 cases reported life threatening outcomes. In most of the CAERS cases, there was

insufficient information reported and it was not possible to determine whether a causal connection existed between the use of melatonin and the AEs reported because of the considerable number of other ingredients in the melatonin product and/or due to the use of concomitant medications.

b. Clinical trials assessing safety

Adverse Events reported in trials of melatonin in patients with primary and secondary sleep disorders

Besag et al. conducted a systematic review of the literature for AEs associated with melatonin and identified controlled clinical trials that administered exogenous melatonin for primary or secondary sleep disorders in children and in adults. In the studies included in the systematic review, the daily melatonin doses ranged from 0.15 mg to 12 mg.[26] Of note, the type, frequency, or severity of AE rates were not correlated with either dose or formulation (immediate/fast-release or controlled/prolonged-release) (Besag et al. 2019).

Subjects in the studies included in the systematic review were monitored for up to 29 weeks, but most studies were of much shorter duration (4 weeks or less). Table 6 shows the most common AEs in the pooled controlled studies and these include headache, daytime sleepiness, other sleep-related AEs (described as red eyes, vivid dreams, and nightmares), dizziness, and hypothermia. Uncommon or rare potential events include gastrointestinal complaints: vomiting, abdominal pain, diarrhea; anxiety, irritability, reduced alertness (concentration impaired), confusion (disorientation); seizures and mild tremor (movement disorders). Similar AEs were also observed in the open-label studies: headache (9.2%), fatigue/asthenia (3.1%), gastrointestinal illness (3.0%), sleepiness (2.6%) and dizziness (1.5%).

[26] The study characteristics including the study design, patient demographics, melatonin formulation and co-medication for the included studies in the systematic literature review can be accessed at: https://link.springer.com/article/10.1007/s40263-019-00680-w#Sec23; Supplementary material 1 (DOCX 66 kb).

Table 6: Adverse Events Reported in Clinical Studies (Numerical and Percentage Frequencies for Melatonin and Placebo Groups) (Besag et al. 2019)

Adverse event	No. studies	Melatonin subjects with AE (AE_{MLT})	Placebo subjects with AE (AE_{PLB})	Subjects with AE corrected for placebo ($AE_{MLT} - AE_{PLB}$)	AE frequency (%) corrected for placebo
Daytime sleepiness[a]	9	50	23	27	1.66
Headache	15	44	32	12	0.74
Other sleep-related AEs[b]	6	21	9	12	0.74
Dizziness	4	14	2	12	0.74
Hypothermia[c]	2	14	4	10	0.62
Decreased appetite	3	7	1	6	0.37
Restlessness	2	6	0	6	0.37
Rash[d]	4	15	9	6	0.37
Burping	1	5	0	5	0.31
Tearfulness	1	5	0	5	0.31
Fatigue	3	25	21	4	0.25
Seizures (not increased rate)	2	12	8	4	0.25
Insomnia[e]	4	7	4	3	0.18
Gastrointestinal illness/diarrhoea	3	10	7	3	0.18
Muzziness/fuzzy feeling/hung-over	3	3	0	3	0.18
Hyperactivity	2	4	1	3	0.18
Enuresis	1	3	0	3	0.18

MLT=Melatonin; PLB=Placebo.
[a] Some of the studies specified 'daytime sleepiness' and others simply stated 'sleepiness' (or similar) but since it is unlikely that night-time sleepiness after the melatonin dose would have been listed as an AE, these have been categorized together as 'daytime sleepiness';
[b] Including 'red eyes,' 'vivid dreams' and nightmares; [c] Including 'cold feelings'; [d] Including skin irritation and pruritus; [e] Including 'poor sleep'

Esposito et al. reviewed the literature and included the most frequently reported adverse effects associated with the use of melatonin in children. These included morning drowsiness, headache, dizziness, diarrhea, rash, hypothermia, and increased enuresis; a mild and transient headache and gastrointestinal symptoms may occur during the first days of treatment (Esposito et al. 2019).

There were no deaths or life-threatening AEs identified in the systematic literature review. There were very few reported AEs considered to be serious or of clinical significance. These included agitation, fatigue, mood swings, nightmares, skin irritation and palpitations. Adverse events reported in the controlled clinical trials of melatonin for primary or secondary sleep disorders were characterized as generally infrequent, mild, or moderate in severity and were either self-limiting or resolved on withdrawal of treatment. Although there were descriptions of AEs associated with exacerbation of pre-existing condition (e.g. worsening migraine), exacerbation of clinical features characteristic of the study population (e.g. agitation and mood swings in patients with ADHD, autism spectrum disorder or other developmental or behavioral disorders), there was no information indicating relatedness to melatonin treatment. One clinical study included in the systematic review reported heart palpitations in a single patient with a pacemaker, which led to withdrawal of the drug but was also considered unrelated to melatonin.

Adverse Events reported in the product marketed for use in adults in the United Kingdom
Section I. Introduction, section of this review discussed three melatonin products marketed outside the United States for use in adults. Besag et al. reported that the adverse reactions in the systematic review analyses and that were listed in the product characteristics (prescriber

information) for Circadin and the side effects listed in the guidance for melatonin provided by the British National Formulary are similar in frequency and nature (Besag et al. 2019). Of note, the British National Formulary site could not be accessed, and it is only available to users in the UK.

Like the marketed sedative-hypnotics, Circadin has moderate influence on the ability to drive and use machines. There are no other safety related warnings or precautions.

Adverse Events reported in the product marketed for use in children with autism spectrum disorder in the United Kingdom

Section I. Introduction, section of this review discussed one melatonin prolonged-release (controlled-release) product marketed as a minitablet outside the United States for use in pediatric patients with autism spectrum disorder (Slenyto). Table 7 and Table 8 summarized the safety data from the clinical study that supported the product approval, which was a randomized, placebo-controlled study in children diagnosed with autism spectrum disorders and neurodevelopmental disabilities caused by SMS who had not shown improvement after standard sleep behavioral intervention. For the pooled melatonin doses during the double-blind period the AE rates compared to placebo were: somnolence (melatonin=28%; placebo=12%), fatigue (melatonin=25%; placebo=18%), agitation (melatonin=18%; placebo=11%) and headache (melatonin=13%; placebo=6%). The rates of mood swings reported as AEs were no different between the treated groups.

Table 7: Most Commonly Reported Treatment Emergent Adverse Events with Slenyto in Pediatric Patients with Autism Spectrum Disorder (Malow et al. 2021)

TABLE S2 Most Commonly Reported Treatment-Emergent Adverse Events (AEs) (Safety Set)

	Double-blind phase (13 weeks)				Open-label phase (91 weeks)	
	PedPRM		Placebo		All PedPRM	
	Participants (n = 60)	Events	Participants (n = 65)	Events	Participants (n = 95)	Events
Participants with at least 1 TEAE	51 (85.0%)		50 (76.9%)		80 (84.2%)	
Total number of AEs		208		156		524
AEs reported by ≥10% participants						
Somnolence	17 (28.3%)	18	8 (12.3%)	8	24 (25.3%)	31
Rate of somnolence events per participant per 1 year of treatment[a]		1.2		0.49		0.19
Fatigue	15 (25.0%)	19	12 (18.5%)	13	25 (26.3%)	33
Rate of fatigue events per participant per 1 year of treatment[a]		1.27		0.8		0.20
Mood swings	10 (16.7%)	10	11 (16.9%)	12	17 (17.9%)	24
Rate of mood swings events per participant per 1 year of treatment[a]		0.67		0.74		0.14
Upper respiratory tract infection	9 (15.0%)	9	7 (10.8%)	8	14 (14.7%)	24
Vomiting	8 (13.3%)	11	10 (15.4%)	10	20 (21.1%)	33
Agitation	11 (18.3%)	12	7 (10.8%)	8	8 (8.4%)	10
Headache	8 (13.3%)	8	4 (6.2%)	4	12 (12.6%)	12
Cough	7 (11.7%)	7	5 (7.7%)	5	16 (16.8%)	27
Dyspnea	6 (10.0%)	6	4 (6.2%)	4	10 (10.5%)	10
Rash	3 (5.0%)	3	3 (4.6%)	3	10 (10.5%)	10

Note: PedPRM = pediatric prolonged-release melatonin; TEAE = treatment-emergent adverse event.
[a]Rate = number of observed events for the entire group divided by 13 (double-blind) or 91 (open-label), which equals the number of events for the entire group by week. This value is divided by the number of participants in the group to provide the number of events per week per participant. The value is multiplied by 52 (weeks/year) to determine the number of events per year of treatment per participant.

Table 8: Most Commonly Reported Severe Adverse Events with Slenyto In Pediatric Patients with Autism Spectrum Disorder (Gringas et al. 2017)

	Double-Blind Phase	
	PedPRM	Placebo
	Patients (n = 60) n (%)	Patients (n = 65) n (%)
Number of patients with at least one severe AE	13 (21.7)	13 (20.0)
Most common AEs		
Agitation	5 (8.3)	3 (4.6)
Fatigue	4 (6.7)	2 (3.1)
Mood swings	3 (5.0)	5 (7.7)

Note: Includes severe AEs reported by ≥5% patients in any group. PedPRM = pediatric-appropriate prolonged-release melatonin minitablets.

The safety of the prolonged-release (controlled-release) melatonin minitablets (2, 5, or 10 mg) was evaluated in a 104-week long-term safety follow on study in N=80 study participants after completing the double-blind controlled efficacy study period and was discussed in the referenced publication (Malow et al. 2021). This study also evaluated the effects of prolonged-release melatonin treatment on sleep, growth, body mass index, and pubertal development.

No deaths were reported during the open label long-term period of the study. Similar types of AEs reported during the double-blind study were observed during the open label study (Table 7). The most frequent treatment-related AEs during the open label period were somnolence (25.3%), fatigue (26.3%), and mood swings (17.9%).

The study authors commented that although somnolence and fatigue were commonly reported, these were reported only once by a participant at some time during the treatment period, most commonly within a short time after dose escalation, and was much less commonly reported during the open label period. The authors considered treatment-related somnolence and fatigue to reflect the pharmacological effect of residual daytime melatonin most probably secondary to the excessive dose, and that it was possible that some of these participants were poor metabolizers of CYP1A2 enzyme and developed daytime somnolence or fatigue owing to melatonin accumulation.

Changes in mean weight, height, body mass index, and pubertal status (Tanner staging done by a physician) were within normal ranges for age with no evidence of change in body mass index or delay in pubertal development.

Melatonin and effects on reproductive function (including effects on growth hormone, luteinizing hormone, follicle stimulating hormone and prolactin)
The potential consequences of long-term exposure to higher than normal melatonin levels for age on alterations in estrogen, testosterone, follicle-stimulating hormone, luteinizing hormone, or prolactin are not known. There was no data on the interaction between melatonin and growth hormone and the effect of exogenous melatonin on normal growth hormone profiles (Besag et al. 2019).

Melatonin and effects on sexual maturation (puberty)
Because endogenous melatonin levels in humans sharply decline just before the onset of puberty there may be a potential risk of delayed sexual maturity and with gonadal development in pre-pubertal children taking melatonin over extended periods, and animal studies have supported this theory (Besag et al. 2019). Following a 1-week dose finding portion of the clinical study, the long-term observational phase assessed Tanner stages in N=69 children who used oral melatonin for an average of 3.1 years (van Geijlswijk et al. 2010). Three Tanner score questions were surveyed (the age at first ejaculation in boys, the ages of menarche of their mothers and the first ejaculation of their fathers) and compared the results with healthy population-based controls. There were no endocrine assessments performed. Only 33% of the children reached the age of 13 in the study, and only 62% of the boys and 91% of the girls answered the questions.
The authors concluded that puberty onset appeared to be undisturbed after 3.1 years of melatonin usage. No differences were detected during the initial trial or follow-up period.

A review by Boafo et al. provided a comprehensive summary of the effects of melatonin on pubertal timing and whether there was disruption of puberty in patients receiving long-term melatonin treatment. The systematic literature review reported that there was insufficient and inconclusive data with conflicting results that exogenous melatonin interfered with normal pubertal development in humans (Boafo et al. 2019).

The long-term study in children and adolescents with autism spectrum disorder discussed above reported no delay in sexual maturation/pubertal development (Tanner assessments) with orally administered prolonged-release (controlled-release) melatonin in a subpopulation of N=31 participants (out of N=80) 8 to 17 years of age after 2 years of continuous use (see Table 9; Malow et al. 2021).

Table 9: Pubertal Development and Change from Baseline in Mean Standard Deviation Scores at Week 106 in Children >8 Years of Age Treated with Pediatric Prolonged-Release Melatonin (Malow et al. 2021)

Pubertal Development and Change From Baseline in Mean Standard Deviation Scores at Week 106 in Children ≥8 Years of Age Treated With Pediatric Prolonged-Release Melatonin (PedPRM)

	PedPRM group				Placebo group			
SDS	**Mean (SD)**	**Range**			**Mean (SD)**	**Range**		
Pubic hair growth	0.881 (1.11), n = 19	−0.43 to 3.04			1.323 (0.998), n = 12	−0.43 to 2.63		
Breast development	0.709 (1.16), n = 7	−0.12 to 3.14			NA	NA		
Genitalia development	0.692 (0.96), n = 12	−0.55 to 2.12			1.205 (0.8), n = 12	−0.55 to 2.11		
Change from baseline	**Mean (SD)**	**Range**	**(95%CI)**	***p***	**Mean (SD)**	**Range**	**(95%CI)**	***p***
Pubic hair growth	1.09 (1.24), n = 16	0.0 to 3.40	(0.49, 1.69)	< .0001	1.55 (1.11), n = 11	0.0 to 2.85	(0.85, 2.35)	< .001
Breast development	1.78 (1.70), n = 5	0.0 to 3.54	(0.21, 3.36)	< .001	NA	NA	NA	NA
Genitalia development	0.74 (1.09), n = 11	0.0 to 2.99	(0.05, 1.43)	< .001	1.30 (1.00), n = 11	0.0 to 2.48	(0.67, 1.94)	< .001

Besag et al. commented that there are yet to be determined effects of prolonged exposure to supraphysiological levels of melatonin on sexual maturation, fetal development, and neonatal development. The significance of melatonin in neonatal development has yet to be clarified, although the greater number, and wider distribution, of melatonin receptors in infants indicates a potentially pivotal role during the early childhood (Besag et al. 2019).

Therefore, the study authors recommend a more conservative policy when treating pre-pubescent children and pregnant or breast-feeding women. The absence of data on long-term safety in pre-pubertal children has led to a consensus among healthcare practitioners that ***melatonin should not be recommended as a first-line treatment for chronic sleep disorders in pre-pubertal children*** (Besag et al. 2019; Buckely et al. 2020). However, this recommendation appears to be based on lack of data rather than firm evidence for an effect of melatonin on puberty.

<u>Melatonin and effect on seizures</u>

Low endogenous melatonin levels have been reported in some patients with epilepsy, and melatonin supplements have improved sleep in these patients, purported to be from GABA receptor agonism. There are conflicting clinical study reports in the literature with inconclusive information regarding melatonin use associated with seizure episodes in patients with epilepsy. A systematic review of the literature reached the same findings reported in a Cochrane review (Brigo et al. 2016), which found that studies of the safety and anticonvulsant effect of melatonin in patients with epilepsy were of insufficient methodological quality to perform a meta-analysis, and no firm conclusions could be drawn regarding any association between supplemental

melatonin and a reduction in seizure activity or that there is an increased risk of seizures (Besag et al. 2019).

Melatonin and cardiovascular effects

The systematic review included discussions about cardiovascular effects on patients using melatonin reported in two studies. There were changes in blood pressure and heart rate in patients with preexisting cardiovascular conditions who were taking antihypertensive medication (nifedipine) together with melatonin with information suggesting possible drug-drug interaction although the authors state that it was not possible to determine conclusively whether the cardiovascular effects resulted from a direct effect of melatonin, or from interaction with cardiovascular medication. Although in the studies in patients without preexisting cardiovascular conditions, there appeared to be no information suggestive of cardiovascular abnormalities with melatonin (Besag et al. 2019).

Dose dependency for adverse events

Besag et al. included information from two clinical trials that analyzed for evidence of dose dependency for any adverse reactions. Two studies compared melatonin at different doses (Van der Heijden et al. 2007 and van Geijlswijk et al. 2010). Van der Heijden et al. found that there was no difference in the rates of AEs between 3 mg and 6 mg daily doses, while van Geijlswijk et al. found that higher body weight adjusted doses (0.15 mg/kg and 0.1 mg/kg) were associated with a greater frequency of AEs than a lower dose (0.05 mg/kg) although the AE frequencies were considered to be low for all three doses.

Residual morning effects

Melatonin has the potential for residual morning effects for daytime sleepiness. Besag et al. discussed that the effects of daytime sleepiness may extend to impaired psychomotor function and increased reaction times, highlighting the importance of appropriate timing of doses. In the clinical studies that reported daytime drowsiness, the symptoms of daytime sleepiness appeared to resolve when the subjects used melatonin at the recommended regular times at bedtime implying that melatonin administration too late may be associated with daytime sleepiness (Besag et al. 2019).

In the Slenyto clinical study the pharmacological activity of the product appeared to wane off after stopping the active treatment. Like the reported observations with Circadin in adult patients with insomnia, melatonin discontinuation was reported to be not associated with withdrawal effects or rebound insomnia with Slenyto exposure in children and adolescents (Malow et al. 2021).

Summary of Adverse Events Data and Clinical Trials Assessing Safety

- Melatonin appears to be a relatively safe substance for oral administration at the nominators' proposed dose 0.2 mg – 5 mg when used for the short-term treatment in children and adolescents with autism spectrum disorders including other neurodevelopmental disorders. Pediatric melatonin safety/tolerability trials are limited but there is no evidence that short-term melatonin use has SAEs. The SAEs with melatonin use was confounded by concomitant medication/disease state, or lacked enough details precluding the ability to determine a drug-event association. The AEs also

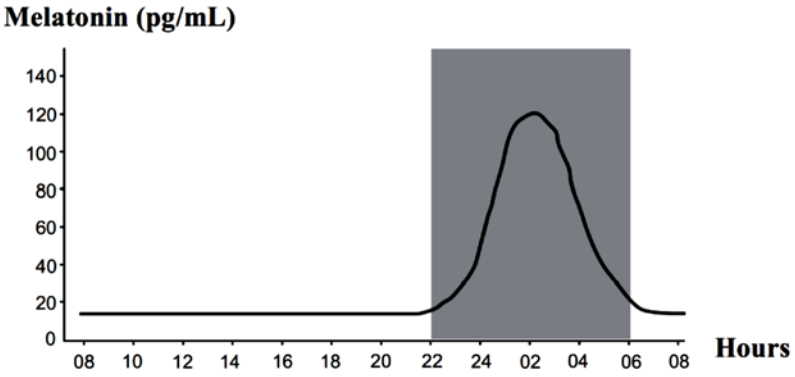
primarily consisted of acute reactions to exposure rather than exposure data for longer-term effects.

- The most frequently reported AEs included somnolence and daytime sleepiness that are expected considering the known mechanism of action and therapeutic use of melatonin i.e., to induce sleep.
- Less frequent AEs were reported related to nausea/vomiting, abdominal pain, dizziness/vertigo, tachycardia, hypothermia, headache, hallucination, irritability, agitation, mood swings, vivid dreams, nightmare (parasomnia), CNS depression, reduced alertness (concentration impaired), confusion (disorientation), seizures and mild tremor (movement disorders). Many of these AEs have also been reported with the approved sedative hypnotics.
- The AEs primarily consisted of acute reactions to exposure rather than exposure data for longer-term effects to determine the safety of long-term melatonin use, particularly in children. Most AEs either resolved spontaneously within a few days with no adjustment in melatonin, or immediately upon withdrawal of treatment.
- The effect of melatonin on sleep is dependent on the dose and the time of administration for managing sleep disorders. In the clinical studies that reported daytime drowsiness, the symptoms of daytime sleepiness appeared to resolve when the subjects used melatonin at the recommended regular times at bedtime implying that melatonin administration too late may be associated with daytime sleepiness.
- Overall there was an increasing trend over time of SAE cases reported to the FAERS database and with rising numbers of reports to the AAPCC NPDS suggesting increased use of melatonin use.
    - There are conflicting clinical study reports in the literature with inconclusive information regarding melatonin use associated with seizure episodes in patients with epilepsy.
    - There was a report of a woman who experienced complex sleep behaviors after consuming melatonin for two weeks. She was hospitalized for developing aggression, anorexia, insomnia, altered mental status and behavioral changes including agitation, and somnambulism (CAERS report ID #151616).
      The reaction appears similar to the information in the label for the marketed sedative hypnotics.
- Melatonin discontinuation was reported to be not associated with withdrawal effects or rebound insomnia with Slenyto exposure in children and adolescents.
- None of the cases reported included information regarding the use of a compounded melatonin product.
- There is no standard dose recommended for melatonin use in adults and in children and there is no information on body weight dosing recommendations. The significant numbers of reports of unintentional exposures and therapeutic errors reported in children may be due to the lack of adequate guidance and dosing recommendations in the pediatric population from adequate and well controlled studies.
    - An infant death was reported in the literature when melatonin was used a sleep aid that was attributed to dosing error suggesting lack of adequate guidance.
      See discussion above in the summary of FAERS database findings and the literature reports.

c. Pharmacokinetic (PK) data

Melatonin plays a key role in regulating the sleep–wake circadian rhythm (Esposito et al. 2019). The suprachiasmatic nucleus in the hypothalamus regulates melatonin synthesis and secretion. The timing of melatonin production is influenced by the retinal perception of light and the endogenous rhythmicity of neurons within the suprachiasmatic nucleus, which controls the pineal gland via neural signals with nearly 80% of the melatonin synthesized at night; peaking in the middle of the night between 2:00 AM and 4:00 AM in the morning as shown in Figure 7 below (Tordjman et al. 2017). With the onset of darkness, melatonin diffuses out of the pineal gland into the blood stream and cerebrospinal fluid, rapidly raising human plasma melatonin levels from about 10-20 pg/ml during daylight hours to 100–200 pg/ml during the hours after sundown (***endogenous melatonin***).

Figure 7: Circadian Profile of Melatonin Plasma Concentrations (Tordjman et al. 2017)

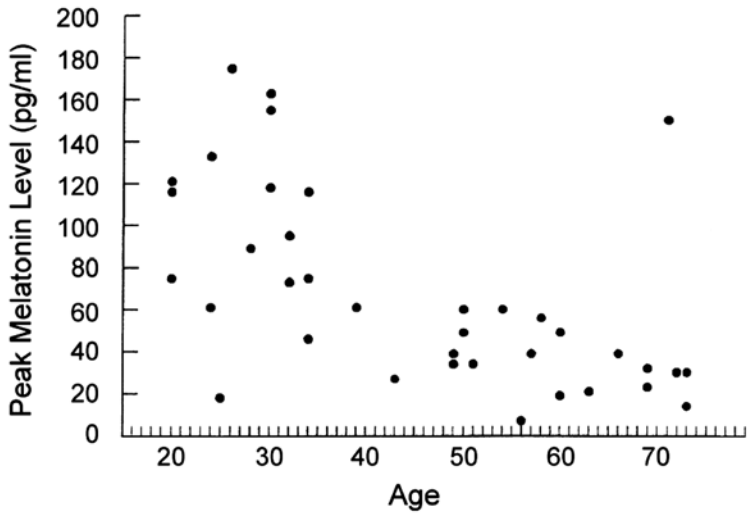


(The shaded area represents the hours after sundown).

Melatonin secretion by the human pineal gland exhibits a pronounced age dependence with melatonin concentrations extremely low during the first 3 months of life. Melatonin concentrations then abruptly increase and contribute to consolidating the sleep–wake rhythm of infants until their own circadian system matures (Esposito et al. 2019).

Endogenous nocturnal melatonin levels are lower in adults than in children; peak nocturnal melatonin levels in most 70-year-olds are only a quarter or less of what they are in young adults, which is due more to their greater body size than a reduction in pineal secretion (Wurtman 2005). Figure 8 below shows night-time peak serum melatonin levels in subjects of different ages.

Figure 8: Night-Time Peak Serum Melatonin Levels in Subjects of Different Ages (Years). (Wurtman 2005)



Studies report significant variability in melatonin levels with ***exogenous*** melatonin administration. Because the different dosage forms have different effects on absorption, distribution, metabolism and excretion (ADME) of active pharmaceutical ingredients (APIs) ***melatonin metabolism affects the PK based on the dosage form and, in particular, melatonin bioavailability appears to be low and variable*** (Moroni et al. 2021).

Most of the melatonin in circulation is inactivated in the liver. It undergoes hydroxylation to 6-hydroxymelatonin (first oxidized to 6-OH-melatonin and then conjugated to sulfate or glucuronide before being excreted into the urine or feces), with about 2–3% excreted unchanged into the urine or saliva.

In a recent systematic review of the clinical pharmacokinetics of melatonin, the following conclusions were reached (Harpsøe et al. 2015):

- The time to reach the maximum concentration (T_{max}) was 50 minutes following ***oral immediate-release*** formulations of melatonin.
- $T_{1/2}$ was 45 minutes in both the oral and IV routes of administration. C_{max}, AUC, Cl, and VD varied extensively between studies.
- Bioavailability of oral melatonin was generally low (approximately 15%) and with significant intra-individual variability.

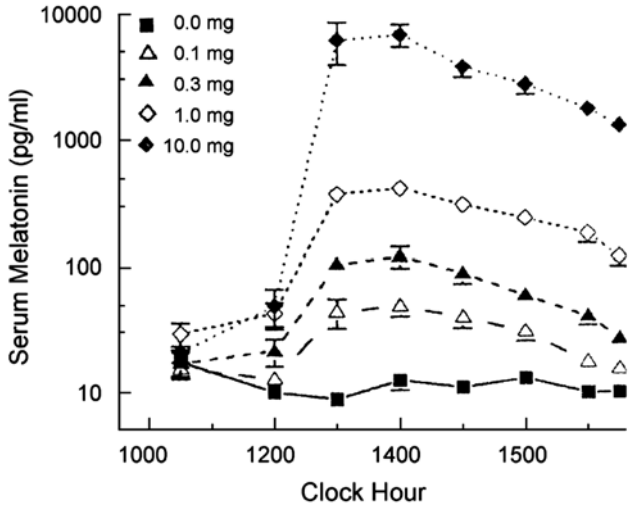
Within 1 hour of the ingestion of between 1 to 5 mg, melatonin concentrations are 10–100 times higher than their physiological nocturnal peak and return to basal levels in 4 to 8 hours (Esposito et al. 2019). The literature reported that food did not change *endogenous* levels of melatonin; nor was there acceptable evidence that any food contains more than trace amounts of the hormone (Wurtman 2005). The Circadian ***prolonged-release*** formulation product characteristics (prescriber information) included information that the rate of melatonin absorption and maximum (or peak) serum concentration (C_{max}) following Circadin 2 mg oral administration was affected by food. The presence of food delayed the absorption of the melatonin resulting in a

prolonged time to reach the maximum concentration (T_{max}=3.0 h versus T_{max}=0.75 h) and lower peak plasma concentration (C_{max}) in the fed state.

The PK profiles in the studies discussed below further show the variability in melatonin levels and present the effects of adding exogenous melatonin during the daytime, not necessarily mimicking the subject's normal circadian profile of (endogenous) melatonin plasma concentrations.

- When 20 healthy male volunteers (mean age = 23 years old) were dosed with oral melatonin (0.1, 0.3, 1, 10 mg) or placebo at 11:45 am in five 8-hour testing sessions (with at least 5 days between sessions) the mean melatonin serum levels of exogenous administered melatonin 0.3 mg dose simulated nocturnal physiological melatonin levels. The levels varied in proportion to the different melatonin doses ingested. The subjects self-reported sleepiness and fatigue (See Figure 9 below; Dollins et al. 1994).

Figure 9: Mean Seum Melatonin Levels for Different Doses Adminsitered During Daytime (Dollins et al. 1994)



- In 12 normal healthy volunteers, the absolute bioavailability of oral melatonin 2 mg and 4 mg was approximately 15%, i.e., oral melatonin tablets in dosages of 2 and 4 mg showed poor absolute bioavailability, either due to poor oral absorption, large first-pass metabolism, or a combination of both (see Table 10 below; DeMuro et al. 2000).

Table 10: Pharmacokinetics of Three Doses of Melatonin

Table I Pharmacokinetics of Three Doses of Melatonin

Dose	AUC (ng•min/ml)	C_{max} (pg/ml)	t_{max} (min)	Half-Life (min)	Bioavailability
2 mg oral	237.77 ± 149.79	2175 ± 1645	52.0 ± 31.5	60.8 ± 13.2	0.143 ± 0.07
4 mg oral	530.57 ± 267.29	5766 ± 2731	60.3 ± 31.6	65.0 ± 11.3	0.159 ± 0.06
2 mg IV	1631.61 ± 425.74	96,850 ± 55,024	1.79 ± 1.41	59.5 ± 7.2	1.00 ± 0.0
p-value[a]	0.0001	0.0001	0.0001	0.385	0.0001

AUC, area under the serum concentration versus time curve from zero to infinity; t_{max}, time to peak concentration; C_{max}, peak serum concentration.
a. IV versus either oral phase.

- When oral melatonin 10 mg was administered to 12 normal healthy volunteers, the absolute bioavailability of oral melatonin 10 mg was only 3% but demonstrated substantial inter-individual differences (Andersen LPH et al. 2016).
- In a PK study administering melatonin 20 µg (0.02 mg) intravenously initially and 500 µg (0.5 mg) orally on a second occasion to four male subjects, peak oral plasma melatonin levels varied from 480 to 9200 ng/L (i.e., 480 to 9200 pg/ml) and the bioavailability of the oral melatonin (determined by comparing the intravenous and oral data) was relatively poor (mean, 33%) and also varied among the subjects, i.e., 10% to 56%. The wide range of bioavailability of melatonin was attributed to the considerable person-to-person variability (Di WL et al. 1997).
- In a PK study that dosed five subjects at 11:00 AM with oral melatonin 80 mg, the individual levels varied by 25-fold among subjects and the peak serum melatonin levels were observed at 60-150 minutes after administration, ranging from 350 to 10,000 times those occurring physiologically at nighttime (Waldhauser et al. 1984). The authors considered the significant differences in the individual levels were to be due to individual differences in the absorption of melatonin.
- Healthy older subjects (mean age = 59 years old) administered microcrystalline cellulose filled gelatin capsule oral dose of melatonin 0.3 mg exhibited three times higher plasma melatonin levels (C_{max}), with correspondingly greater variability, than young adults (mean age = 25 years old) who received the same dose (Zhdanova et al. 2001).
- Fourteen healthy young male volunteers were administered one oral melatonin 80 mg capsule at noon, 1:00 pm and 2:00 pm (total oral melatonin dose 240 mg; the highest dose used in the studies included in this review). Their plasma melatonin levels increased at least 1000-fold over basal levels in 60 minutes; however, the time to reach the maximum concentration (T_{max}) was comparable with studies that used lower doses. There was no significant change in serum levels of growth hormone, thyroid stimulating hormone or cortisol. Elevated serum prolactin levels were observed, which was an effect not observed with a physiologic melatonin dose (Waldhauser et al. 1987).

The effect of melatonin on sleep is dependent on the dose and the time of administration for managing sleep disorders.

In a double-blind, placebo-controlled crossover PK/pharmacodynamics (PD) study conducted in six healthy volunteers, each subject received three different doses of melatonin (0.05 mg, 0.5 mg, 5 mg) and placebo, each only once at 17:00 hours and the effect of range of low doses of oral melatonin on various sleep parameters on the night following treatment were assessed. Visual analogue scales (VAS) for sleep quality and subjective alertness and daily sleep logs were used to estimate sleep onset, latency and the number and duration of night awakenings. There was increase in plasma melatonin profiles with a dose-dependent response (see Figure 10 below). Based on the subjective sleep measurements there was an earlier sleep onset for all three doses of melatonin, improving sleep quality and reduced duration of night awakenings (see Figure 11 below), with mean values showing a dose-dependent response (Deacon and Arendt 1995).

Figure 10: Mean Serum Melatonin Levels for Different Doses Adminsitered During Sundown (Deacon and Arendt 1995)

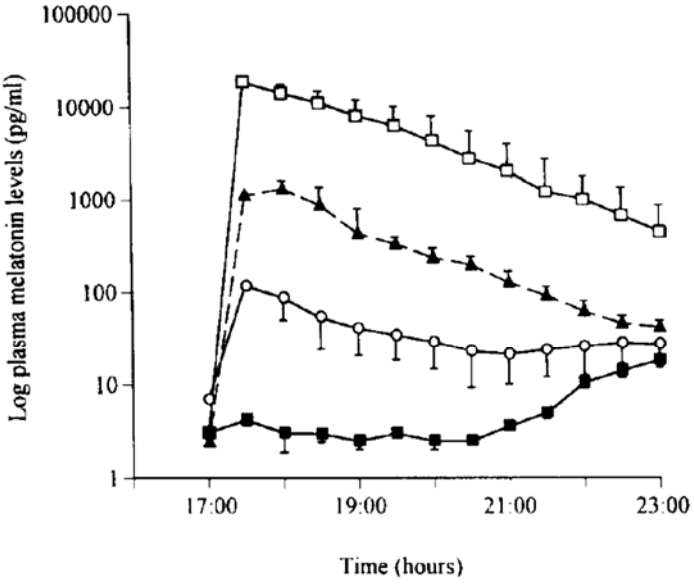
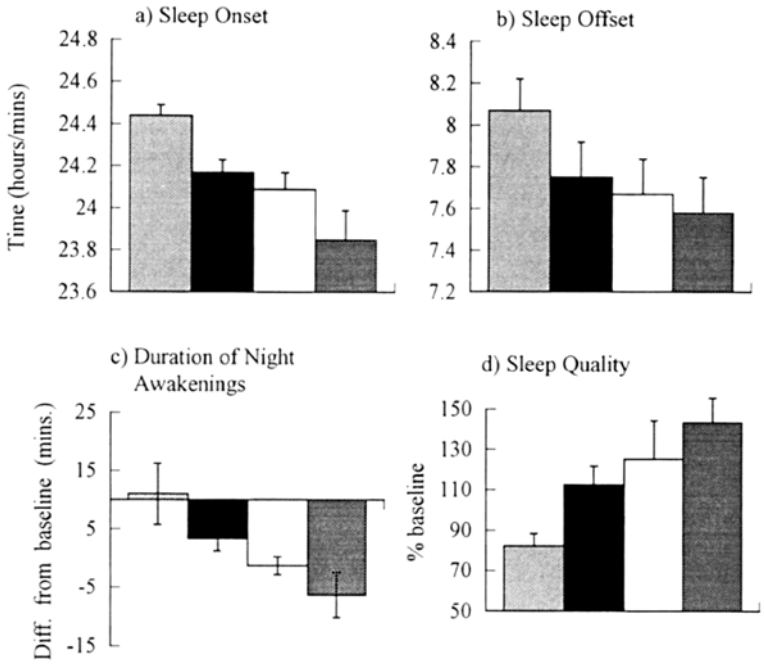


Fig. 1. Mean(±S.E.M.) plasma melatonin profiles for 6 subjects after oral administration of 5 mg (□), 0.5 mg (▲), 0.05 mg (○) of melatonin (in corn oil) or placebo (■) at 17:00 h on day 3.

Figure 11: The Effect of Oral Melatonin on Sleep Parameters on the Night Following Treatment (Deacon and Arendt 1995)



Subjective sleep measurements for the first night following late afternoon treatment with placebo (single-line shading), 0.05 mg (■), 0.5 mg (□), 5 mg (double-line shading) melatonin.

Even though a PD effect of melatonin was seen at doses included in the study discussed above, a dose-dependent effect was **not** demonstrated when six healthy volunteers received placebo, or low doses of melatonin (0.3, or 1.0 mg immediate-release melatonin) at three fixed times in the evening and around bedtime (18:00, 20:00 and 21:00) in a total of nine sessions, each with a 4 to 7 days period between sessions. They also reported an absence of melatonin sleep-promoting effects when the melatonin was dosed at 21:00 hours. The authors concluded that the effects of low doses of melatonin on sleep induction in healthy volunteers depend, at least partially, on the time of its administration (Pires et al. 2001).

It should be noted that the previously discussed PK studies of melatonin were conducted in young, healthy adults; thus, the PK profiles from these studies present the effect of adding a single dose of ***exogenous*** *immediate-release melatonin* on top of the subject's normal circadian profile of melatonin plasma concentrations (see Figure 7 above; Tordjman et al 2017). However, a single evening dose of immediate release melatonin may not mimic the normal physiological (***endogenous***) production or the release of melatonin throughout the night in children with neurodevelopment disorders because they do not appear to have a normal physiological production of melatonin. In one study by Melke et al, low plasma melatonin concentrations (defined as at least half the mean of the control values) occurred in 65% of 258 patients with autism spectrum disorders (Melke et al. 2008).

Kulman et al evaluated serum levels of melatonin every four hours in 14 children aged 5-10 years with untreated autism spectrum disorders and none of them showed a normal melatonin circadian rhythm. These children had significantly lower mean concentrations of melatonin, during the dark phase of the day (i.e., from 8pm to 8am), with respect to the values observed in the controls (Kulman et al. 2000). This may explain why there was no effect on total sleep time or number of awakenings when a single dose of *immediate release exogenous melatonin* was administered to N=35 children with neurodevelopmental disabilities and sleep impairment in the three studies reviewed by Phillips and Appleton in 2004. The authors stated that a slow or sustained-release preparation may potentially improve these components of sleep and increase the total sleep time (Phillips and Appleton 2004).

Interactions Between Melatonin and Other Drugs

Exogenous melatonin may increase the effects of other hypnotics and there may be associated greater detrimental effect on psychomotor performance and memory. A possible PK interaction with the antidepressant citalopram in one patient resulted in severe sedation (See also CAERS *Report ID #148686* discussed in Section II.B.2.a. about patient melatonin reaction with citalopram). Besag et al reported that concomitant use of GABAergic antiepileptic drugs, including sodium valproate, may be associated with suppressed endogenous melatonin levels. Benzodiazepines have also been shown to exert an inhibitory effect on nocturnal melatonin secretion. The possibility of augmented effects when melatonin is taken with other central nervous system depressants is also indicated (Besag et al. 2019).

Melatonin is primarily metabolized by CYP1A2 and CYP2C19, and so inhibitors of CYP1A2 may increase melatonin concentrations (Esposito et al. 2019). The British National Formulary warns of a severe risk of interaction with fluvoxamine and a theoretical risk of interactions with the antibacterial ciprofloxacin and rifampin, caffeine, combined hormonal contraceptives,

leflunomide, mexiletine, phenytoin, ritonavir and teriflunomide. Drug-drug interactions are additionally discussed in the prescriber information for the EMA approved U.K. marketed prolonged-release products Circadian, Slenyto, and melatonin Pharma Nord immediate-release tablet for jetlag (EMA assessment of Circadin 2007; EMA Assessment of Slenyto 2018).[27]

Summary of Pharmacokinetics

- Endogenous melatonin levels vary by age and depend on the time of day for peak secretions. Furthermore, the nocturnal endogenous melatonin levels in patients with neurodevelopmental disorders are lower than in normal healthy individuals experiencing sleep disorders. Therefore, the pharmacological effects of exogenous melatonin on the PD aspects of sleep in these populations may not be the same as populations experiencing other primary pediatric sleep disorders. This may explain why there was no overall effect on total sleep time or the number of awakenings in children with neurodevelopmental disabilities and sleep impairment with certain doses of orally administered immediate release melatonin.
- Melatonin has low oral bioavailability (approximately 15%). The effect of exogenous melatonin on its PD effects on sleep is dependent on the dose and the time of administration for managing sleep disorders. Orally administered immediate-release formulations of melatonin reach maximum concentration (T_{max}) around 50 minutes whereas prolonged-release formulations have variable PK and PD effects on sleep.
- The risk of drug interactions involving melatonin has yet to be quantified, although there is some evidence that CYP1A2 inhibitors may result in elevated serum levels of melatonin. The British National Formulary warns of a severe risk of interaction with fluvoxamine and a theoretical risk of interactions with the antibacterial ciprofloxacin and rifampin, caffeine, combined hormonal contraceptives, leflunomide, mexiletine, phenytoin, ritonavir and teriflunomide.

d. Availability of alternative approved therapies that may be as safe or safer

Alternative therapies for sleep disorders in children and adolescents with autism spectrum disorder and other neurodevelopmental disorders

There is no FDA approved treatment for pediatric insomnia and sleep disorders in children and adolescents with autism spectrum disorder or other neurodevelopmental disorders.

Treatments that may be safer than melatonin for the management of sleep disorders include non-pharmacological interventions like cognitive behavioral therapy, behavioral interventions, and maintaining adequate sleep hygiene.

Please also see Section II.C.3. regarding the effectiveness of alternative approved therapies.

Conclusions: Low doses of melatonin that include the nominators proposed dose ranges from 0.2 mg to 5 mg for use as compounded melatonin for oral administration appear to be relatively safe for the short-term treatment of sleep disorders (sleep initiation) in children and adolescents with neurodevelopmental disorders. The SAEs were confounded by concomitant

[27] The Melatonin Pharma Nord summary of product characteristics (prescriber information) can be accessed at https://www.medicines.org.uk/emc/product/11018/smpc.

medication/disease state, or lacked enough details precluding the ability to determine a drug-event association. Pediatric melatonin safety/tolerability trials are limited but there is no evidence that short-term melatonin use has SAEs. Alternative treatments (discussed above) are recommended that may be safer than melatonin for the initial management of sleep disorders.

There is paucity of data from long-term trials regarding the safety of continuous melatonin treatment over extended periods or about the potential risks in at-risk and special populations. The literature recommends that practitioners take a more conservative approach when treating pre-pubescent children and pregnant or breast-feeding women with melatonin. The systematic literature reviews reported that there was insufficient and inconclusive data with conflicting results that exogenous melatonin interfered with normal pubertal development in humans, although the long-term safety study of prolonged-release (controlled-release) melatonin dosage form in children and adolescents with autism spectrum disorder reported no delay in sexual maturation/pubertal development (Tanner assessments).

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

For purposes of discussion of the use of melatonin in insomnia and sleep disorders, in Section C.1., information to evaluate treatment effect is limited to children and adolescents with autism spectrum disorder and other neurodevelopmental disorders. Please see Apendix 1, for a summary discussion regarding the use of melatonin for the treatment of primary sleep disorders in adults and in children.

<u>Sleep outcomes and definitions discussed in the section</u>
The clinical studies discussed in this section include information for objective assessments for the sleep outcomes that were derived from either actigraphy and/or polysomnography. The following information was obtained from the referenced American Academy of Neurology (AAN) practice guideline published in 2020 (Buckley et al. 2020).

Sleep onset latency (SOL) refers to the amount of time from lights turned off until the onset of any sleep stage. Normal SOL in adults is less than 20 minutes. In children, sleep latency is estimated at 10–26 min, depending on study methods. Sleep latency does not change between childhood and adolescence (Zolovska and Shatkin 2013). Prolonged sleep latency would be characterized as difficulty falling asleep.

Night awakenings refers to the number of complete awakenings occurring after sleep initiation.

Total sleep time (TST) refers to sleep duration during a given sleep period time (usually at night). Reduced TST relates to prolonged SOL, night awakenings, and early-morning waking. Included studies compare TST changes with treatment rather than referencing age-specific sleep duration recommendations.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of melatonin for treatment of insomnia and sleep disorders in the pediatric population with neurodevelopmental disorders*

    a. Pediatric Insomnia and Sleep Disorders

Up to 40% of typically developing children and adolescents have sleep problems, although these often lessen with age (Buckley et al. 2020). The prevalence of pediatric insomnia varies from 1 – 6% in the general pediatric population (Gringras et al. 2017).

Up to 80% of children with neurodevelopmental disorders: autism spectrum disorder, ADHD, cerebral palsy; neurogenetic disorders like Rett syndrome, tuberous sclerosis, Angelman syndrome, Williams syndrome, and SMS are affected by disrupted sleep, which frequently has deleterious effects on their daytime behavior, cognition, growth, and overall development (Esposito S. 2019). The etiology of sleep disorders in children with neurodevelopmental disorder is highly heterogeneous and disease specific.

Sleep disorders in children and adolescents (McDonagh et al. 2019)
Healthy children (ages 6 to 12) typically fall asleep within 20 minutes of going to bed, wake one to three times per night and usually sleep 8.0 to 9.5 hours (McArthur and Budden 1998). Sleep disorders have been used to describe difficulties with falling asleep (i.e., sleep initiation) and staying asleep (Parker et al. 2019). Children with pediatric insomnia experience repeated difficulty in getting to sleep (more than 30 min per night), insufficient sleep (less than 8 h), and poor sleep consolidation or quality despite having the age-appropriate time and opportunity to sleep, all of which lead to daytime functional impairment for both patients and their families (Esposito et al. 2019). Sleepiness in children may manifest as irritability, behavioral problems, learning difficulties, motor vehicle crashes (teenagers), and poor academic performance (Esposito et al. 2019). Disordered sleep is also associated with daytime behavioral disturbances, increased injury risk, obesity, and poor academic performance in the general pediatric populations (Buckley et al. 2020). Table 11 shows the normal parameters of sleep in children and adolescents and to differentiate normal sleep pattern from frequent sleep disturbances.

Table 11: Normal Sleep Parameters in Children and Adolescents (Esposito et al. 2019)

Age	**Total Sleep Time**	**Naps (on average)**
0-2 months	16 – 18 h	3.5 per day at 1 month of age
2-12 months	12 – 16 h (Most children aged 6–9 months sleep throughout the night)	Two per day at 12 months of age
1-3 years	10 – 16 h	One per day at 18 months of age
3-5 years	11 – 15 h	50% of 3-year-olds do not nap
5-14 years	9 – 13 h	5% of whites and 39% of blacks nap at 8 years of age
14-18 years	7 – 10 h	Napping at this age suggests insufficient sleep or a possible sleep disorder

Insomnia and sleep disorders may be caused by gastrointestinal and pain-related diseases, pulmonary diseases such as asthma or chronic cough, and upper airway pathologies, especially snoring and obstructive sleep apnea (OSA), atopic dermatitis. Delayed sleep–wake phase disorder is often observed in adolescents which is a type of circadian disorder characterized by a tendency to go to bed late and difficulties in waking up. Table 12 shows the characteristics of the primary pediatric sleep disorders.

Table 12: Common Sleep Disorders in Children (Esposito et al. 2019)

Sleep disorder	Epidemiology	Clinical features	Diagnostic criteria	Treatment options
Obstructive sleep apnea	Prevalence: 1–5% Onset: 2–8 years of age M:F = 1:1 More frequent in blacks and people with craniofacial abnormalities, Down syndrome, neuromuscular diseases, or choanal atresia	Snoring Unusual sleep positions Sleep-related paradoxical breathing Bedtime enuresis or diaphoresis Morning headaches Cognitive/behavioural problems Excessive daytime sleepiness Enlarged adenoids and tonsils Pectus excavatum	PSG apnea–hypopnea index > 1.5 per hour	Adeno-tonsillecto-my CPAP, nasal steroids, rapid maxillary expansion
Confusional arousals	Prevalence: 17.3% in 3–13-year-olds, 2.9–4.2% in children older than 15 years M:F = 1:1 Positive family history	Sleep drunkenness Unusual behaviour Slowed responsiveness Slurred speech Confused after awakening Occurs during the first half of the sleep period, no memory of the event	History	Re-assurance Increase total sleep time Scheduled awakenings Bedroom/home safety counselling
Sleep terrors	Prevalence: 1–.5% Onset: early childhood M:F = 1:1	Intense fear Difficulty in awakening from episode Dangerous activities Occurs during the first half of the sleep period, no memory of the event Overlap with other parasomnias	History	Re-assurance Increase total sleep time Scheduled awakenings Bedroom/home safety counselling -Benzo-diazepines
Nightmares	Prevalence: 10–50% in 3–5-year-olds Onset: 3–6 years of age; peaks: 6–10 years of age M:F = 1:1	Unpleasant dreams Increased sympathetic activity Occurs during the second half of the sleep period, memory of the event Reluctance to sleep increases Association with mood disorders or post-traumatic stress disorder	History	Re-assurance Increase total sleep time Scheduled awakenings Bedroom/home safety counselling Cognitive behavioural therapy, SSRI (off-label use)
Behavioural insomnia of childhood	Prevalence: 10–30% M:F = 1:1	Sleep-onset association type Limit-setting type	History	Prevention, parental education, and extinction techniques
Delayed sleep phase disorder	Prevalence: 7–16% in adolescents Onset: adolescence Positive familiar history in 40% of cases	Difficulty in falling asleep and waking up at socially acceptable times Night owl	History Sleep diary and/or actigraphy for at least 1 week	Sleep hygiene education Regular sleep–wake schedule Avoid bright lights before bedtime Melatonin Bright light therapy Use of sleep logs to monitor progress
Restless legs syndrome	Prevalence: 2% More common in F Positive familiar history	Urge to move legs with discomfort Begins in the evening, worsens with rest, eases with movement Association with iron deficiency Association with negative behaviour and mood, and decreased cognition and attention Increased prevalence in children with ADHD	History PSG Presence of two of the following: disturbed sleep; a first-degree relative with the condition; five or more periodic limb movements per hour of sleep during PSG	Avoid nicotine and caffeine Dis-continue offending medications Iron replacement in the case of deficiency Severe cases: levodopa, dopamine agonists, gabapentin

PSG polysomnography, *CPAP* continuous positive airway pressure, *M* males, *F* females, *SSRI* selective serotonin re-uptake inhibitors, *ADHD* attention deficit/hyperactivity disorder

Sleep disorder in children and adolescents with neurodevelopment disorders

For children with neurodevelopmental disorders, sleep disorders are more common and more severe compared with typically developing children. The sleep disorders observed in 13–86% of patients with neurodevelopmental disorders are reported to be complex and usually more difficult to treat than in subjects without neurodevelopmental disorders (Esposito et al. 2019).

Co-existing conditions in children with neurodevelopmental disabilities such as epilepsy, nocturnal gastroesophageal reflux disorder, anxiety, depression, bipolar disorder, psychosis, and ADHD can further contribute to sleep disorder. Circadian disorders with altered melatonin profiles are frequently seen in children with neurodevelopmental disorders, for example in children with SMS. Altered endogenous melatonin profiles have also been reported in patients with Down syndrome, Prader-Willi syndrome, and Sanfilippo syndrome (Esposito et al. 2019).

Difficulty falling asleep (40%), maintaining sleep (35%), difficulty in settling at night (51%) and nocturnal awakenings (67%) are common sleep complaints in children with neurodevelopment disorders. In some severe cases, fragmented sleep throughout the day and night induces daytime sleepiness and an irregular sleep schedule that may lead to a free-running sleep rhythm or to a complete reversal of the night-day cycle (Bruni et al. 2019).

Autism spectrum disorders

Autism spectrum disorders (ASD) are complex neurodevelopmental disorders characterized by core ASD symptom clusters in 2 domains: social interaction/communication challenges and restrictive, stereotyped, or repetitive behavior patterns. ASD affects more than five million Americans with reported prevalence in the United States of 1 in 59 children (approximately 1.7% children). Because of the heterogeneity of symptoms and severity in ASD, it may be diagnosed in children at different ages (Hyman et al. 2020).

Co-occurring conditions are common in children and adolescents with autism spectrum disorders and may have significant effects on their health and quality of life, family functioning and clinical management. Co-occurring medical and behavioral conditions include disorders of sleep and feeding, gastrointestinal tract symptoms, obesity, seizures, ADHD, anxiety, mood disorders, and wandering that affect the child's function and quality of life.

Between 44% and 83% of children with autism spectrum disorder are reported to experience sleep disorders (Wright 2011), in comparison to 10–20% of typically developing young children (Ramachandani et al. 2000). Children with autism spectrum disorder including other neurodevelopmental disorders are more likely to experience chronic sleep problems than their age-matched typically-developing peers.

Sleep disorders in children and adolescents with autism spectrum disorders include difficulties initiating and maintaining sleep, frequent and prolonged night awakenings, irregular sleep–wake patterns, short sleep duration, and early morning awakening (Buckley et al. 2020). They experience hyperarousal and hypersensitivity to environmental stimuli that contributes to insomnia. Adolescents are more likely to have shorter sleep duration, experience daytime sleepiness, and delayed sleep onset compared with younger children with autism spectrum disorders, who are more likely to have bedtime resistance, experience parasomnias, and night awakening. Reasons for the increased frequency of sleep disturbances in children and youth with autism spectrum disorders may include differences in melatonin metabolism, developmental disruption of other neurotransmitter systems critical to sleep, and lack of social expectations, among other explanations (Hyman et al. 2020).

Smith-Magenis syndrome

Smith-Magenis syndrome (SMS) is a genetic disorder caused by a microdeletion involving the retinoic acid-induced 1 (RAI1) gene that maps on the short arm of chromosome 17p11.2 or a pathogenic mutation of RAI1. SMS affects at least 1 in 25,000 individuals globally but is likely underdiagnosed and may have a true prevalence closer to 1 in 15,000 individuals (Kaplan et al. 2020).

Smith-Magenis syndrome affects patients through numerous congenital anomalies, intellectual disabilities, behavioral challenges, and sleep disorder. Sleep disorders in patients with SMS typically present in infancy and persist throughout adulthood, and can include frequent nocturnal arousals, early morning awakenings, and excessive daytime sleepiness. The sleep disorder associated with SMS are attributed to haploinsufficiency of the RAI1 gene. One consequence of reduced function of RAI1, and characteristic of Smith-Magenis syndrome, is an ***inversion of the circadian rhythm***; higher endogenous melatonin levels are seen during the day than during the night resulting in a diurnal melatonin secretion rather than nocturnal pattern (Bruni et al. 2019; Kaplan et al. 2020).

Practitioners treating sleep disorders in patients with SMS use a combination of sleep hygiene techniques, over the counter supplemental melatonin, and/or off-label use of medications such as β1-adrenergic antagonists, pharmaceutical grade melatonin, melatonin receptor agonists, and stimulant medications, to improve sleep outcomes. Typically, the off-label pharmacotherapy reported includes a combination of a β1-adrenergic antagonist administered in the morning, which decreases daytime plasma melatonin levels with additional (exogenous) melatonin treatment at night, which restores plasma circadian melatonin rhythm and enhances sleep (Bruni et al. 2019).

b. Melatonin for treatment of insomnia and sleep disorders in the pediatric population with autism spectrum disorders and other neurodevelopmental disorders

Although melatonin is not a component of any FDA-approved product, it is the most frequently used treatment for insomnia and sleep disorders in the pediatric population with autism spectrum disorders and other neurodevelopmental disorders reported in several literature reviews. Melatonin is available to consumers over the internet and in retail stores in the United States. A survey of pediatricians reported that 25% had recommended melatonin for pediatric insomnia in children with and without neurodevelopmental disorders (Parker et al. 2019).

Table 13 described clinical studies reported with melatonin use in the literature that were analyzed in systematic reviews, some of which included meta-analysis of the independent studies. These studies were assessed to evaluate melatonin for the treatment of insomnia and sleep disorders in the pediatric population with autism spectrum disorders and other neurodevelopmental disorders. The clinical studies that were included for evaluation in Table 13 were also discussed in the AAN practice guideline for the treatment of insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder (Buckley et al. 2020).

The studies included in Table 13 showed a treatment response in favor of melatonin for the sleep outcomes evaluated when used in the short term. In the systematic reviews that analyzed data from controlled trials, melatonin decreased sleep onset latency (median 28 minutes; range 11-51 minutes), increased sleep duration or total sleep time (median 33 minutes; range 14-68 minutes), and increased the wake time after sleep onset (range 12-43 minutes), but with no improvement in the number of awakenings per night (range 0-2.7) (mean difference data shown in Table 14 and Table 15) (McDonagh et al. 2019). The improvements in total sleep time while

on melatonin treatment appeared to be due to earlier sleep onset. Adding behavioral intervention to melatonin treatment resulted in a better treatment response.

There was melatonin treatment effect compared with placebo for measures of total sleep time and sleep onset latency; however, the exact extent of the benefit and whether there were groups of children who benefited the most are unclear (Figure 12 and Figure 13). There was no difference in the mean number of night awakenings with melatonin compared with placebo in the autism spectrum disorder population or in the populations with other neurodevelopmental disorders.

The studies included in Table 13 used either actigraphy data as objective measure of sleep or used parents reported and recorded entries in the sleep diaries. The sleep diary included weekly reporting form that asked the parents to note specific sleep-related events daily. Literature reports suggest the parent report diaries have correlation to actigraphy. Actigraphy is a non-invasive method used to study sleep–wake patterns by assessing movement, provides continuous monitoring of activity level that can be translated to valid estimates of sleep–wake measures (Cortesi et al. 2012). There may be issues with interpreting data from the crossover design studies included in the analyses because of the duration of the washout period between treatments, whether that has any effect of interventions on sleep patterns and the circadian rhythm, and the biases due to patients/parents' prior treatment experiences. However, considering there is not enough data from randomized controlled trials, data from crossover studies and open-label studies were included. The study citations discussed below are chronologically organized.

Table 13: Melatonin Treatment for Sleep Disorders in Children and Adolescents with Autism Spectrum Disorders (Clinical Studies) (Buckley et al. 2020; Hyman et al. 2020)

Referenced Study Title **Trial design**	**Population**	**Regimen/Schedule/Route**	**Efficacy Outcomes**
Garstang, J and M Wallis, 2006, Randomized Controlled Trial of Melatonin for Children with Autistic Spectrum Disorders and Sleep Problems, Child Care Health Dev, 32(5):585-589.			
Randomized, double-blind, placebo-controlled, crossover trial, with 4 weeks treatment period. Parents recorded the baseline sleep pattern daily using sleep diary for one week prior to receiving the first treatment. Sleep diary recorded total sleep time, sleep latency, night awakenings and morning awakening. The trial started in January 2003 and completed in December 2004.	**N=11** children between 4 and 16 years old with reported prior diagnosis of ASD (DSM criteria not specified), with history of difficulties in sleeping at night defined as sleep onset latency of at least 1 h after desired bedtime or night awakenings that required parental attention, persisting at least four nights a week during the last 6 months and be causing distress to the child or other family members. There also had to be a failure of behavioral management techniques.	Two treatment periods. Melatonin 5 mg or placebo for 4 weeks. There was a washout period of 1 week between each of the treatment periods before administering the alternative investigational product (crossover). Unable to ascertain whether melatonin used was immediate release or extended release/prolonged release.	Seven children completed the trial although it is not clear how many children were in each treatment group. In the small study sample compared to placebo treated children melatonin reduced mean sleep latency by up to 1 h, reduced number of night awakenings and increased the mean total sleep time by 1 h. See cross-referenced Table 14 for results.
Wright, B, D Sims, S Smart, et al., 2011, Melatonin Versus Placebo in Children with Autism Spectrum Conditions and Severe Sleep Problems Not Amenable to Behaviour Management Strategies: A Randomised Controlled Crossover Trial, J Autism Dev Disord, 41(2):175-184.			
Randomized, double-blind, placebo-controlled, crossover trial, with 3 months treatment period. Parents recorded the baseline sleep pattern daily using sleep diaries for one month prior to receiving the first treatment. Children previously on melatonin were not included.	**N=17** children between 4 and 16 years old with diagnosis of ASD based on WHO (ICD-10) research diagnostic criteria (DSM criteria not specified), with reported difficulties in sleeping at night defined as excessive time establishing sleep (sleep latency), excessive night-waking or reduced total sleep time. There also had to be a failure of	Two treatment periods; 9-month study. There was a washout period of 1 month between each of the treatment periods before administering the alternative investigational product for another 3 months (crossover). Melatonin (***standard/immediate release***) was initiated at 2 mg capsule or placebo for three months administered 30–40 min before planned sleep time. The dose may be increased by the parent every three nights by 2 mg to a maximum dose of 10 mg. If ‘‘good’’	In the seventeen children who completed the trial, the baseline average sleep latency was 135 min, the average number of night awakenings was 0.5 and the total sleep time was 499 min. Compared to placebo treated children, melatonin reduced mean sleep latency by 47 min (95% CI, −78.50 to −14.90), increased the mean total sleep time by up to 52 min (95% CI, 19.3–5.47), although

Referenced Study Title Trial design	Population	Regimen/Schedule/Route	Efficacy Outcomes
During treatment, parents used the sleep diaries daily to record total sleep time, sleep latency, night awakenings and morning awakening.	behavioral management techniques.	sleep was achieved the child was stabilized at that titrated dose. ‘‘Good’’ sleep was defined as an improvement of 50% or better.	there was no change in number of night awakenings. See cross-referenced Table 14 for results. The mean final dose when on the melatonin arm was 7 mg and ranged from 2 to 10 mg.
Malow, BA, RL Findling, CM Schroder, et al., 2021, Sleep, Growth, and Puberty after 2 Years of Prolonged-Release Melatonin in Children with Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 60(2):252-261 e253.			
Open-label, 17-week dose-escalation study of melatonin for insomnia in children with ASD. During the 1-week baseline and two-week acclimation phase prior to receiving the first treatment study participants underwent actigraphy evaluations. During the two-week acclimation phase, parents gave their children an inactive (compounded) liquid 30 min before bedtime that was flavored similar to supplemental melatonin, in order to acclimate the child to taking a liquid medication before bedtime.	**N=24** children between 3–10 years with ASD (DSM-IV-TR diagnosis), with parent reported sleep onset delay of 30 min of longer on three or more nights per week.	Each study participant was initially given 1 mg (4 ml) ***liquid supplemental nutrition melatonin (Natrol, Chatsworth CA)*** for 3 weeks for up to 14 weeks of melatonin dosing. If a satisfactory response occurred, defined as falling asleep within 30 minutes in five or more nights/week (for at least one of the weeks) as documented by actigraphy, melatonin was continued at its current dose until the end of the 14-week dosing period. If a satisfactory response did not occur at the preceding 1 mg dose, escalation to next dose was permitted at 3-week intervals, (starting at 3 mg x 3 weeks, then 6 mg and next up to 9 mg) until a satisfactory response was documented by actigraphy.	Compared to baseline assessments, at the end of the 14-week treatment period, melatonin reduced mean sleep latency by 16 min, increased the mean total sleep time by up to 15 min. Most children received doses up to 3 mg, and three children were treated with 6 mg.
Cortese, S, F Wang, M Angriman, et al., 2020, Sleep Disorders in Children and Adolescents with Autism Spectrum Disorder: Diagnosis, Epidemiology, and Management, CNS Drugs, 34(4):415-423.			
Randomized, double-blind, placebo-controlled, 12 weeks treatment trial. Parents recorded the baseline sleep pattern daily using sleep diaries during the 14-day run-in period prior to receiving the first treatment. Trial participants had	N=134 children between 4–10 years with ASD (DSM-IV-TR diagnosis), experiencing sleep onset insomnia and impaired sleep maintenance.	Trial participants were assigned randomly to one of four treatment arms, either (1) combination of controlled-release melatonin 3 mg and cognitive–behavioral therapy (N=35); (2) ***controlled-release melatonin*** 3 mg (**N=34**); (3) four sessions of cognitive–behavioral therapy (N=33); or (4) placebo (N=32) for 12 weeks in a 1:1:1:1 ratio.	Treatment response was assessed with sleep diary and sleep questionnaire. 1-week actigraphy monitoring was performed at baseline and at week 12. Changes were compared to the baseline measurements.

Referenced Study Title Trial design	Population	Regimen/Schedule/Route	Efficacy Outcomes
seven consecutive nights of actigraphy evaluations at baseline and at 12-week for primary outcome reassessment. Participants met at the outpatient clinic every 2 weeks for a 15 minute meeting to report adverse effects and to obtain the dosage pills for the following 2 weeks.		The investigational melatonin was described as high purity melatonin preparation (99.9%). The high-purity melatonin released 1 mg immediately and 2 mg over 6 hours. *Of note, controlled-release melatonin is also referred to* as *prolonged-release melatonin*.	Compared to placebo treated children, melatonin reduced mean sleep latency by 38 min, increased the mean total sleep time by up to 68 min, with reductions in number of night awakenings. Melatonin therapy alone was more effective than cognitive–behavioral therapy alone or placebo in improving bedtime resistance, sleep onset delay, night awakenings and sleep duration subscales. See cross-referenced Table 14 for results.
Gringras, P, T Nir, J Breddy, et al., 2017, Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 56(11):948-957 e944. The two-year long-term safety follow on study to the controlled efficacy study (Gringas et al. 2017) is discussed in Malow, BA, RL Findling, CM Schroder, et al., 2021, Sleep, Growth, and Puberty after 2 Years of Prolonged-Release Melatonin in Children with Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 60(2):252-261 e253.			
Multicenter, randomized, double-blind, placebo-controlled 13-week trial that was preceded by a 14-day single-blind placebo run-in period. *Of note, the referenced publication is the study that supported product approval in the EMA for melatonin prolonged-release minitablets (Slenyto) for treating insomnia in children and adolescents with ASD, in addition to approval for use in patients with Smith-Magenis syndrome*.	**N=119** children between 2–17.5 years with ASD (diagnosed by ICD–10 or DSM-5 or DSM-IV criteria), with minimum 3 months of impaired sleep, defined as ≤6 hours of continuous sleep and/or ≥0.5-hour sleep onset latency from lights-off on 3 of 5 nights, based on parent reported diary recordings and patient medical history.	Trial participants were administered ***prolonged-release melatonin minitablets*** or identical appearing placebo, starting with 2 mg daily. If the sleep variables assessed at 3 weeks did not improve from baseline by at least 1 hour, as measured by shortening of sleep latency and/or increase in total sleep time, the dose was escalated to 5 mg. Patients then continued double blind on 2 or 5 mg of prolonged-release melatonin minitablets or placebo for the remaining 10 weeks.	Efficacy assessment (recorded in a diary, and actigraphy) included change from baseline in mean sleep scores to week 13. Compared to placebo treated children, melatonin reduced mean sleep latency by 25 min (95% CI -44.7, -5.9), increased the mean total sleep time by up to 32 min (95% CI 2.48, 62.38), with reductions in number of night awakenings. See cross-referenced Table 14 for results.
Sleep Onset Latency (SOL) refers to the amount of time from lights turned off until the onset of any sleep stage.; WASO describes the time individuals spend awake after sleep onset and before sleep offset.; Night awakenings reference the number of complete awakenings occurring after sleep initiation.			

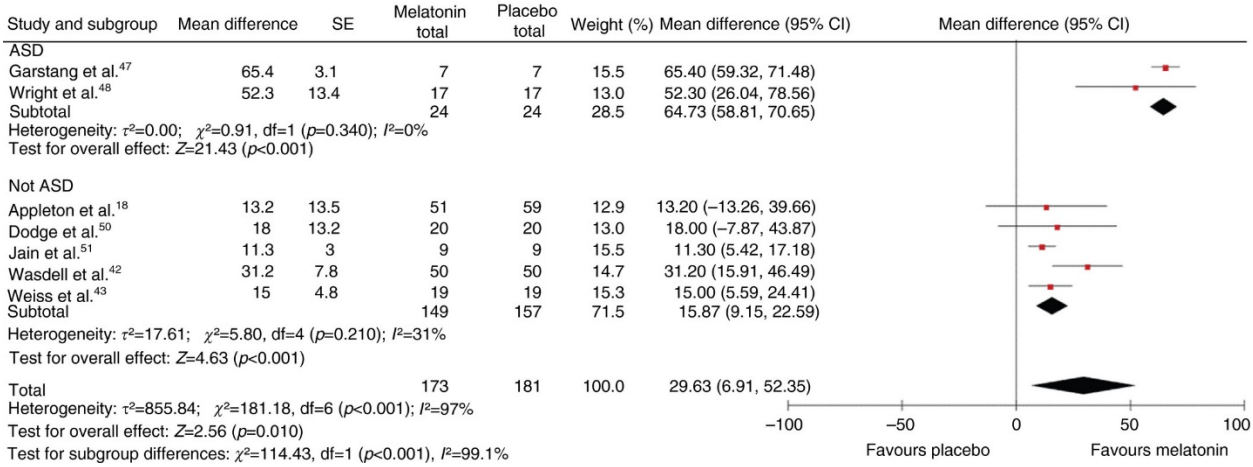
Table 14: Effect of Melatonin on Sleep Outcomes in Children with Sleep Disorders and Autism Spectrum Disorder (McDonagh et al. 2019)

Referenced Study	Dose, mg	N[a]	Duration, week	Mean age, year	Method of assessment	Differences between medication and placebo in mean change from baseline mean difference, min (SD)		
						Sleep onset latency	Sleep duration or total sleep time	Number of awakenings
Garstrang and Wallis, 2006	5	11	4	9	Sleep diary	-51.00 (8.35)	65.00 (14.95)	-0.18 (0.08)
Wirojanan et al, 2009	3	12	2	6	Actigraphy	-28.10 (NR)	21.00 (NR)	-0.07 (NR)
Wright et al, 2011	4-10	17	12	9	Sleep diary	-46.70 (55.00)	52.30 (55.10)	-0.10 (0.40)
Cortesi et al, 2012	5	160	12	7	Actigraphy	-37.40 (NR)	67.59 (NR)	-2.74 (NR)
Gringras et al, 2017	2-5	119	13	8.7	Sleep diary	-25.30 (98.98)	32.43 (152.81)	-0.09 (1.30)

Abbreviations: NR, not reported; SD, standard deviation
[a] N based on number of participants that completed the assessment.

Information shown in Figure 12 below and included in the reference (Parker et al. 2019) show meta-analysis data from seven controlled trials that pooled sleep diary-reported total sleep time: six crossover trials with a washout period (n=122) and one parallel-group trial (n=110) in children with autism spectrum disorder and other neurodevelopmental disorders. There was an increase in sleep diary-reported total sleep time with melatonin treatment compared with placebo in the population with autism spectrum disorder (pooled mean difference 64.73 min, 95% confidence interval (CI) 58.81,70.65). The forest plot treatment effect estimates were all in the direction showing benefit with melatonin. However, in the population with other neurodevelopmental disorders the results were inconsistent and melatonin treatment did not appear to show much improvement in total sleep time (pooled mean difference 15.87, 95% CI 9.15, 22.59).

Figure 12: Sleep Diary-Reported Total Sleep Time (minutes): Melatonin Versus Placebo and Autism Spectrum Disorder (ASD) Subgroup Analysis (Parker et al. 2019)



Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom.

Meta-analysis data from controlled trials that pooled sleep diary-reported sleep onset latency in children with autism spectrum disorder and other neurodevelopmental disorders are shown in Table 14 and Table 15.

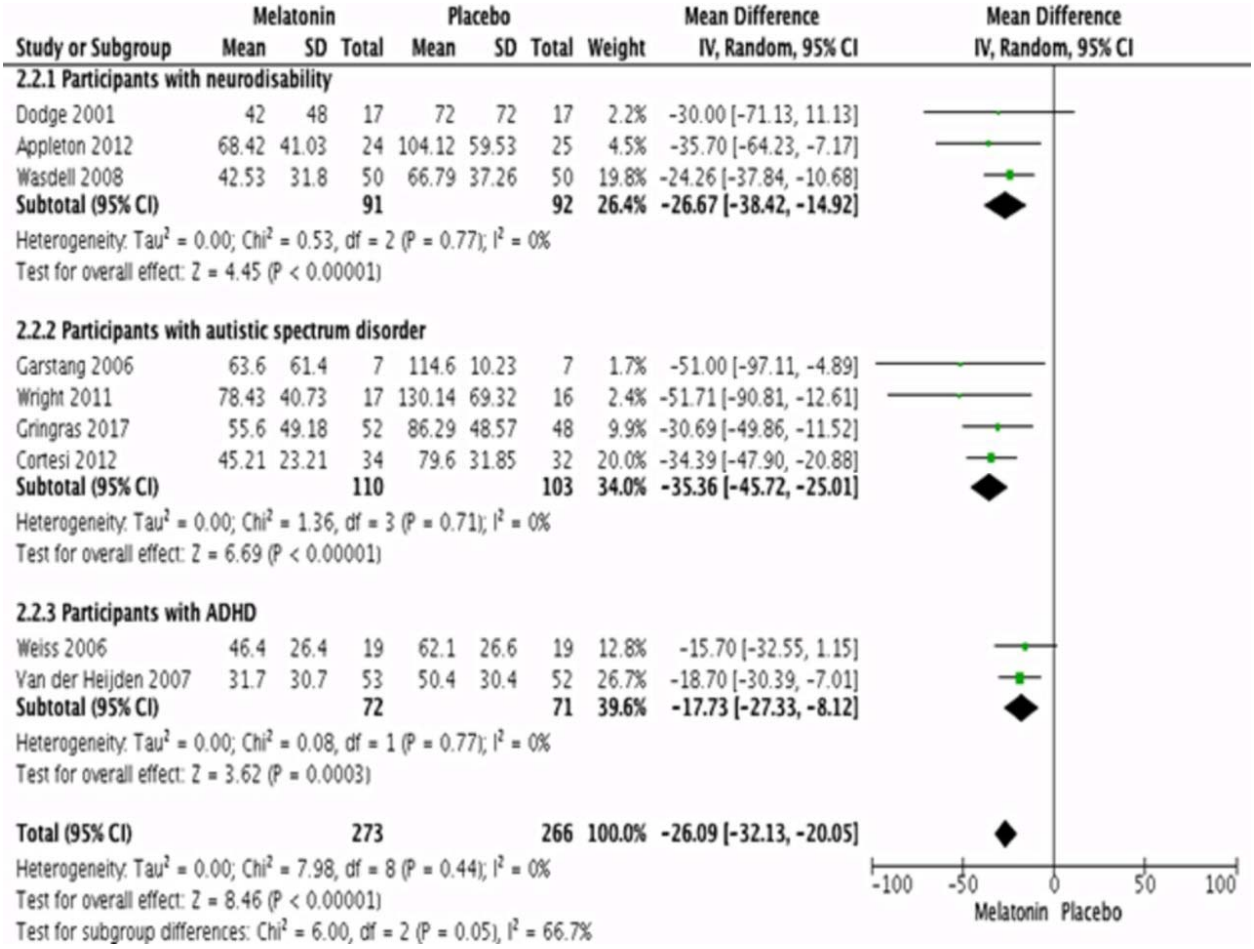
Table 15: Effect of Melatonin on Sleep Outcomes in Children with Sleep Disorders and ADHD or other Neurodevelopmental Disorder (McDonagh et al. 2019)

Referenced Study	Dose, mg	N[a]	Duration, week	Mean age, year	Method of assessment	Differences between medication and placebo in mean change from baseline mean difference, min (SD)		
						Sleep onset latency	Sleep duration or total sleep time	Number of awakenings
Comorbid Attention-deficit/hyperactivity disorder (ADHD)								
Van der Heijden et al, 2007	3-6	107	4	9	Actigraphy	–24.30 (32.36)	33.5 (56.53)	NR
Weiss et al, 2006	5	19	1.4	10	Actigraphy	-16.00 (15.34)	NR	NR
Comorbid other Neurodevelopmental Disorder								
Appleton et al, 2012 *Majority children diagnosed with ASD* [#]	2-12	59	12	9	Actigraphy	-45.34 (83.61)	1.33 (112.92)	NR
Braam et al, 2008 *Children with Angelman syndrome*	2.5-5	8	4	10	Sleep diary	-31.75 (NR)	65.00 (NR)	-0.70 (NR)
Dodge and Wilson, 2001 *Majority children with diagnosis cerebral palsy*	5	20	2	7	Sleep diary	-30.00 (61.19)	18.00 (93.05)	-0.20 (0.70)
Wasdell et al, 2008 *Children with cerebral palsy, epilepsy, severe intellectual loss, autism spectrum disorder* [#]	5	32	1.4	7	Actigraphy	-24.26 (34.64)	23.72 (85.71)	-0.45 (5.12)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; NR, not reported; SD, standard deviation
[a] N based on number of participants that completed the assessment.
[#] No information for number of subjects with each diagnosis.

Additional supportive meta-analysis data from controlled trials that pooled sleep diary-reported sleep onset latency in children with autism spectrum disorder and other neurodevelopmental disorders are shown in the Figure 13 below (Abdelgadir et al. 2018). There was a decrease in sleep diary-reported sleep onset latency with melatonin treatment compared with placebo in the population with autism spectrum disorder (pooled mean difference -35.36 min, 95% CI -45.7, -25.01) and the forest plot treatment effect estimates were all in the direction showing benefit with melatonin. However, in the population with ADHD other neurodevelopmental disorders the results were inconsistent and melatonin treatment did not show a reduction in sleep onset latency.

Figure 13: Sleep Diary-Reported and Actigraphy Sleep Onset Latency (minutes): Melatonin Versus Placebo for Autism Spectrum Disorder (ASD), ADHD and other Neurodevelopmental Disorders (Abdelgadir et al. 2018)



Sleep onset latency defined as the time in minutes from the child being placed in bed to sleep onset. Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom.

Although melatonin is likely being used in children with insomnia and other neurodevelopmental disorders with dosing between 3 to 6 mg of melatonin per night to reduce sleep onset and to increase total sleep duration, studies results are inconclusive and not like the results observed in children with autism spectrum disorder. The studies did not show that melatonin treatment

reduced sleep onset delay or increased total sleep duration in pediatric populations with ADHD and other neurodevelopmental disorders. (Error! Reference source not found.and Table 15). Furthermore, there are no specific clinical guidelines as to how to prescribe melatonin to patients with other neurodevelopmental disorders and there does not appear to be consensus regarding treating sleep disorders in ADHD.

Melatonin was evaluated in two small studies that included **N=21** children with Angelman syndrome. The first was an open-label trial involving thirteen children in whom sleep duration increased during treatment with melatonin 3 mg; the second placebo controlled study in eight children (four on melatonin treatment) reported that melatonin 2.5–5 mg showed shorter sleep onset latencies, earlier sleep onset times, fewer night awakenings, and longer sleep duration in comparison with placebo. However, as shown in Table 15 and Figure 13, there is insufficient information regarding a treatment effect in this population (Abdelgadir et al. 2018).

Rett Syndrome is a rare genetic neurological and development disorder primarily seen in girls causing a progressive loss of motor skills and speech. **N=9** patients with Rett syndrome aged 4-17 years (mean 10.1 ± 1.5 years) were treated with (immediate release) fast-release melatonin 2.5 to 7.5 mg (based upon individual body weight) and placebo in a double blind, placebo controlled, crossover trial. For the 10-week study there was a one-week baseline period, two 4-week treatment periods, and a 1-week washout between the treatments. Sleep was evaluated with a sleep diary and by actigraphy. Baseline sleep quality was poor compared with healthy children, i.e., low sleep efficacy (mean 68.0% ± SE 3.9%), long sleep-onset latency (42.1 ± 12.0 minutes) and a short and fragmented total sleep time (7.5 ± 0.3 hours; 15 ± 2 awakenings per night). Melatonin decreased mean sleep-onset latency by 19.1 ± 5.3 minutes during the first 3 weeks of treatment (with no difference from placebo at Week 4). Melatonin increased total sleep time in the two subjects with the worst initial total sleep time (i.e., 5.5 hours and 6.5 hours), while total sleep time worsened for four subjects and no significant change in total sleep time for three subjects; overall, there was no difference in total sleep time outcome (McArthur and Budden 1998).

The referenced publication in Table 13 and Table 14 above that included 119 children and adolescents evaluating melatonin use in children with autism spectrum disorder also included four children with SMS (Gringras et al. 2017). Patients with SMS also have comorbid autism spectrum disorder. Table 16 below includes information from two open-label studies that evaluated melatonin in N=57 children. The treated children showed slight reduction in sleep onset from baseline and marginal improvements in total sleep time. Of note, melatonin has EMA marketing authorization for use in patients with SMS as melatonin prolonged-release (controlled release) minitablets (Slenyto).

Table 16: Melatonin Treatment for Sleep Disorders in Children and Adolescents with Smith-Magenis Syndrome (Clinical Studies)

Referenced Study Title **Trial design**	**Population**	**Regimen/Schedule/Route**	**Efficacy Outcomes**
***Smith-Magenis syndrome* (SMS)**			
De Leersnyder, H, JL Bresson, MC de Blois, et al., 2003, Beta 1-Adrenergic Antagonists and Melatonin Reset the Clock and Restore Sleep in a Circadian Disorder, Smith-Magenis Syndrome, J Med Genet, 40(1):74-78.			
Open-label, 6-month study of melatonin for insomnia in children with SMS. Parents completed bedtime and daytime diaries for the duration of the study. Actigraphy measures were obtained.	**N=10** children (six boys, four girls, aged 4-18 years) were recruited from the cohort of Smith-Magenis syndrome confirmed children diagnosed at Necker-Enfants Malades Hospital, Paris.	The ten children in the study were administered β1-adrenergic antagonist, acebutolol (10 mg/Kg) early in the morning to suppress endogenous daytime melatonin release, and a fixed dose ***controlled-release melatonin*** 6 mg in a single dose in the evening.	Before drug administration, mean sleep onset was 9:15 pm (range 8:30-10 pm), mean waking time was 5:40 am (range 4 -7 am), and mean duration of sleep was 8.20 hours (range 7.15-9). On melatonin added regimen, mean sleep onset was delayed to 9:45 pm (range 9-11 pm), mean waking delayed to 6:40 am (range 6-8 am), and mean duration of sleep extended to 8.50 hours (range 8-9.30 hours). Actigraphy data showed that children did not wake up during the night and EEG recordings confirmed a more regular sleep stage organization and a rapid access to sleep stage 3-4 (slow wave stage). Sleep was deep and quiet for both children and their family and day/night life was dramatically improved.
De Leersnyder, H, N Zisapel and M Laudon, 2011, Prolonged-Release Melatonin for Children with Neurodevelopmental Disorders, Pediatr Neurol, 45(1):23-26.			
Open-label study up to 33.5 (SD 21.2) months in patients with other neurodevelopmental disorders including patients with Smith-Magenis Syndrome who were in a specialized compassionate-use program in France. Observations were limited to parental reports.	**N=47** children (twenty-two females; twenty-three males) between 10.9 (SD 4.7) years old.	Children received a dose of 2-4 mg of ***controlled-release melatonin*** if the body weight was <40 kg, and 6 mg if the body weight was≥40kg. (mean dose range 4-6 mg)	Within 3 months on melatonin treatment compared with baseline, sleep latency decreased by 44.0% (18.0±12.0 minutes vs 10.00±3.2 minutes), sleep duration increased by 10.1% (8.5±1.2 hours vs 9.4±1.3 hours), the number of awakenings decreased by 75% (0.5%±0.5% vs 2.0%±0.9%,).

The Cochrane Systematic Review of melatonin for non-respiratory sleep disorders in visually impaired children (defined as children with "poor or no vision") stated that no studies fulfilling the inclusion criteria were found; therefore, no outcome data were reported. The authors concluded that there was no high-quality data to support or refute the use of melatonin for sleep disorders in visually impaired children (Khan et al. 2011).

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Melatonin has been evaluated as a bulk drug substance for use in drug products compounded under section 503A intended to treat insomnia and sleep disorder in children and adolescents with autism spectrum disorder. Autism spectrum disorder is a serious medical condition associated with morbidity that has a substantial impact on day-to-day functioning.

Coexisting sleep disorders can worsen the core symptoms of autism spectrum disorders. Poor sleep quality and insufficient nighttime sleep can exacerbate cognitive performance deficits, contributing to negative effects on mood, and behavioral problems (Gringras et al. 2017; Buckley et al. 2020). Core or cooccurring autism spectrum disorder symptoms such as intellectual disability, sensory integration deficits, restrictive and repetitive behaviors, communication deficits, and limited responsiveness to social cues can interfere with sleep training and exacerbate or prolong sleep problems (Esposito et al. 2019). Sleep disorders negatively affect sleep and quality of life of affected individuals and their families. It can have a detrimental impact on the physical and emotional well-being of other family members; for example, children's sleep disturbance is associated with heightened levels of parental stress and irritability (Parker et al. 2019).

3. *Whether there are any alternative approved therapies that may be as effective or more effective.*

Sedative-hypnotic drug products are a class of drugs used to induce and/or maintain sleep[28]. There are no FDA approved treatments for the treatment of insomnia in the pediatric population.

FDA-approved drugs are prescribed off-label for the management of sleep disorders in children and adolescents (e.g., antihistamines, a-adrenergic agonists like clonidine, antidepressants, antipsychotics) for their sedative side effects without sufficient information on its efficacy, safety, or the dosing regimen in these populations (Gringras et al. 2017).

Please also see Section II.B.2.d. regarding the safety of alternative approved therapies.

Conclusions: Autism spectrum disorder is a serious medical condition associated with morbidity that has substantial impact on day-to-day functioning. Co-morbid sleep disorders can have significant effects on their health and quality of life, family functioning and clinical management.

[28] The URL for the referenced FDA webpage accessed on March 01, 2021 can be found at https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information

The studies that were discussed above showed a treatment response in favor of melatonin for the sleep outcomes evaluated when used in the short term in children and adolescents with autism spectrum disorder, albeit the response may be differential based on the melatonin dose, timing of administration and the dosage form, i.e., immediate release compared to the complex formulations that may be controlled-release (prolonged release). In the systematic reviews that analyzed data from controlled trials, melatonin appeared to be of clinical benefit in decreasing sleep onset latency and increasing sleep duration or total sleep time, which are meaningful benefits in the overall health of that child and the wellbeing of that family that includes their caregiver.

The AAN practice guideline for the treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder recommends that clinicians should offer melatonin (pharmaceutical-grade melatonin if available) starting with a low dose *if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed*. The AAN recommended that clinicians counsel children, adolescents, and parents regarding potential adverse effects of the unapproved use of melatonin for the treatment of children and adolescents with sleep disorders and that there is insufficient long-term safety data (Buckely et al. 2020).

In addition, the clinical report from the American Academy of Pediatrics (AAP) guidance for the clinician for the identification, evaluation, and management of children and adolescents with autism spectrum disorder recommends that sleep onset may be aided by treatment with melatonin at doses from 1 to 6 mg and may be maintained with long-acting melatonin (Hyman et al. 2020).

Unlike the treatment effects of melatonin observed in the population with autism spectrum disorder, the results were inconclusive, and the studies did not show that melatonin treatment reduced sleep onset delay or increased total sleep duration in pediatric populations with ADHD and other neurodevelopmental disorders. These inconclusive results may be due to the heterogeneity of the conditions studied and the small numbers of subjects for the various study populations with other neurodevelopmental disorders. As the authors in the referenced publications have discussed, the observed difference in melatonin treatment effects might reflect differences in the etiology of the sleep disturbance in children with autism spectrum disorder compared with children with other neurodevelopmental disorders, with relatively low levels of melatonin reported in children with autism spectrum disorder. Because of the altered physiological levels of endogenous melatonin in populations with neurodevelopmental disorders it is possible that the effectiveness of exogenously administered melatonin treatment may also depend on the dosage form and type of formulation: immediate release versus prolonged release, in addition to the other important variables like the appropriate dose and the timing of administration for achieving optimal treatment benefit and to minimize the residual effects experienced. Furthermore, there are no specific clinical dosing guidelines as to how to prescribe melatonin to patients with the other neurodevelopmental disorders and there does not appear to be consensus regarding treating sleep disorders in ADHD.

Although there is no clear evidence of treatment effect in the clinical studies in the SMS population that may be in part due to the extremely small study sample, the EMA licensed a *prolonged-release* dosage form of melatonin (see Section I. Introduction). It is likely that for managing an inversion of the circadian rhythm that *prolonged-release* melatonin dosage form may be desirable for the intended regulation of circadian rhythm abnormality to maintain nocturnal melatonin levels and sleep pattern together with other treatments administered during the day to suppress endogenous daytime melatonin release and for managing sleep, overall.

D. Has the substance been used historically in compounding?

Databases searched for information on melatonin in regards to Section II.D. of this consultation included PubMed, Natural Medicines, compoundingtoday.com, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

FDA requested current and historical use data for melatonin from the Johns Hopkins University Center of Excellence in Regulatory Science and Innovation (JHU CERSI). This section also references information from the JHU CERSI report (JHU CERSI 2020).

1. Length of time the substance has been used in pharmacy compounding

The nominators did not provide historical use data. Melatonin was discovered from the bovine pineal gland in 1958 by Aaron Lerner and co-workers (Lerner et al. 1958). There is insufficient literature evidence available to determine the length of time melatonin has been used in pharmacy compounding; however, literature suggests that use of melatonin may be increasing (Grigg-Damberger and Ianakieva 2017). The earliest literature found that mentions compounding melatonin in the United States is from 2009 and examined the stability of melatonin in an extemporaneously compounded sublingual solution and hard gelatin capsule (Haywood et al. 2009).

2. The medical condition(s) it has been used to treat

Results from a Google search using the terms *melatonin compounding* indicate that melatonin is/has been used as a bulk drug substance to compound drug products in capsule, extended release capsule, oral drops, mixture, cream, syrup, tablet, dissolvable tablet, sublingual tablet and spray dosage forms. It has also been compounded as a topical formulation to suppress the development of UV-induced skin redness. Many compounding pharmacy websites advertise that their compounded melatonin products support healthy sleep, regulates the body's circadian rhythms and induction of sleep and may have anti-oxidant properties. One compounding pharmacy website[29] claims evidence is emerging that melatonin "may be helpful in reducing the incidence of migraine." Another compounding pharmacy website[30] claims melatonin has numerous functions, including that it affects the release of sex hormones, aids the immune system, helps prevent cancer (by blocking estrogen), decreases cortisol levels, helps balance the stress response, improves mood, improves sleep quality, increases the action of benzodiazepines, stimulates the parathyroid gland, stimulates the production of growth hormone, provides cardio

[29] See https://www.keycompounding.com/melatonin-migrane-prevention/.
[30] See http://www.keystonerx.com/blog/general/mighty-melatonin/.

protection and may decrease the risk of stroke by significantly lowering cholesterol and blood pressure.

The International Journal of Pharmaceutical Compounding (IJPC) has published compounding formulations for melatonin 5 mg/g and progesterone 5 mg/g foam emulsion[31] for hot flashes; melatonin 0.6 mg/mL oral suspension[32], melatonin 1 mg/mL and pyridoxine hydrochloride 0.1 mg/mL oral suspension[33], and melatonin 1 mg/mL and pyridoxine hydrochloride 0.1 mg/mL oral suspension sugar-free (SF)[34] for patients who cannot swallow solid dosage forms, including children with ASD; and melatonin 0.0033% transdermal gel[35], melatonin 1 mg/mL oral suspension SF[36] and melatonin 2 mg/mL oral suspension SF[37] for use as a contraceptive agent, as an adjunct to chemotherapy and for sedation.

3. How widespread its use has been

A Google search indicates that compounding pharmacies in Australia and South Africa compound melatonin pursuant to a prescription.

Melatonin is the most frequently used pharmacological treatment for pediatric insomnia and sleep disorders in children and adolescents with autism spectrum disorder or other neurodevelopmental disorders (Buckley et al. 2020; McDonagh et al. 2019).

The JHU-CERSI report evaluated the current and historical use of six bulk drug substances (inositol, 2,3-Dimercapto-1-propanesulfonic acid, glutathione, melatonin, oxytocin and methylcobalamin) for use in autism spectrum disorder. The report drew on three distinct data resources (clinical, population, and a national sample), supplemented with interviews of key opinion leaders in research and practice. The report's findings regarding melatonin are summarized below.

Use of Melatonin in a Clinical Sample: In a clinical sample of children with autism spectrum disorder under 17 years of age that receive care at Kennedy Krieger Institute (KKI) Center for Autism and Related Disorders (CARD), <10% of parents used melatonin for their child with autism spectrum disorder and all prescriptions were for oral administration.

Use of Melatonin in a Population Sample: In a population of 1,487 parents of children under 18 years of age from the Simons Foundation Powering Autism Research through Knowledge (SPARK) initiative, an online registry of self-referred parents/caregivers of individuals with autism, melatonin was the most frequently used (60%) of the six substances studied and was most often administered orally (96%). Respondents reported that melatonin was most often used to address sleep problems.

[31] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=3441 (subscription required)
[32] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=2303 (subscription required)
[33] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=2838 (subscription required)
[34] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=2839 (subscription required)
[35] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=3392 (subscription required)
[36] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=3396 (subscription required)
[37] See https://compoundingtoday.com/Formulation/FormulaPDF.cfm?FormulaID=3537 (subscription required)

Use of Melatonin in a National Sample: Evaluation of Medicaid claims data from the years 2010-2014 for children with autism spectrum disorder revealed that of the medications assessed, use of melatonin was <1% among children with and without autism spectrum disorder.

Key Opinion Leaders (KOL): Phone interviews with three KOLs, composed of currently practicing physicians and researchers with expertise in autism spectrum disorder and complementary and alternative medicine (CAM), were conducted to obtain a qualitative understanding of the patterns of use and knowledge of the compounded drug substances of interest for autism spectrum disorder in mainstream clinical practice. All three KOLs commonly recommend the use of melatonin to address sleep issues, specifically sleep onset, for their autism spectrum disorder patients. Overall, melatonin was seen as a safe, common treatment used by patients with autism spectrum disorder.

Some limitations of the JHU-CERSI study include recall bias with self-reporting, CMS data not capturing drug utilization paid for by non-Medicaid means and limited number of KOLs interviewed. The JHU-CERSI study is one source of information that we considered among many.

4. Recognition of the substance in other countries or foreign pharmacopeias

A search of the Japanese Pharmacopoeia (17th Edition), British Pharmacopoeia (BP 2020) and the European Pharmacopoeia (10th Edition, 10.3) did not show any listings for melatonin.

As previously discussed, several melatonin containing products are approved outside of the United States. They include Circadin 2 mg prolonged-release tablet and Slenyto 1 mg and 5 mg prolonged-release minitablets approved by the EMA, melatonin 3 mg immediate-release film-coated tablet and melatonin 1 mg/ml oral solution approved in the UK, and Melatobel granules, 0.2% approved in Japan.

Conclusions: Based on internet searches, it appears that compounding pharmacies have been using melatonin as a bulk drug substance to compound drug products in capsule, extended release capsule, oral drops, mixture, cream, syrup, tablet, dissolvable tablet, sublingual tablet, spray, and topical formulation dosage forms. According to the JHU CERSI report that evaluated six substances used for autism spectrum disorder, melatonin is sometimes used as a treatment for sleep disorders in patients with autism spectrum disorder. Melatonin is approved in Europe, Australia and Japan.

III. RECOMMENDATION

We have balanced the criteria described in Section II above to evaluate melatonin for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor of*** melatonin for oral administration being placed on that list based on the following:

1. Melatonin is a small molecule hormone. It is likely to be stable under ordinary storage conditions as a solid. When compounded as proper liquid formulations (e.g., proper compositions, storage under vacuum or inert atmosphere, protected from light), the product is also likely to be stable. The nominated substance is easily characterized with various analytical techniques and the preparation of this substance has been well developed.

2. Melatonin appears to be a relatively safe substance for oral administration at the nominators' proposed dose 0.2 mg – 5 mg for the short-term treatment of sleep disorders in children and adolescents with neurodevelopmental disorders. There is insufficient data from long-term trials regarding the safety of continuous melatonin treatment over extended periods or about the potential risks in at-risk and special populations. The most frequently reported AEs are somnolence and daytime sleepiness that are expected considering the known mechanism of action and use of melatonin i.e., to induce sleep, although children and adolescents with autism spectrum disorder may experience increased agitation. Concomitantly administered CYP1A2 inhibitors may result in elevated serum levels of melatonin. Alternative treatments are recommended that may be safer than melatonin for the initial management of sleep disorders. Non-pharmacological interventions that are safer like cognitive behavioral therapy and behavioral interventions with adequate guidance on maintaining adequate sleep hygiene should be attempted before considering melatonin as a treatment.

3. The available evidence indicates/suggests that melatonin may be effective for the short-term treatment of sleep disorders in children and adolescents with autism spectrum disorder under the supervision and care of healthcare practitioner. Based on the clinical studies discussed in the literature there appears to be a treatment response in favor of melatonin for the sleep outcomes evaluated that appear to be predictive of clinical benefit, albeit the response may be differential based on the melatonin dose, timing of administration and the dosage form. In the systematic reviews that analyzed data from controlled trials, melatonin appeared to be of clinical benefit in decreasing sleep onset latency and increasing sleep duration or total sleep time, which are meaningful benefits in the overall health of that child and the wellbeing of that family that includes their caregiver.

   The effect of exogenous melatonin on its PD effects on sleep is dependent on the dose and the time of administration for managing sleep disorders. Melatonin metabolism also affects the pharmacokinetics based on the exogenous melatonin dosage form administered. Although melatonin may be effective in children and adolescents with autism spectrum disorder, there is insufficient information to support melatonin use in

children and adolescents with other neurodevelopmental disorders, or for the treatment of primary sleep disorders.

4. Melatonin has been used in pharmacy compounding since at least 2009 and has been compounded in a variety of dosage forms. According to the JHU CERSI report, melatonin is sometimes used as a sleep aid in patients with autism spectrum disorder in the U.S. Melatonin is approved for use in Europe, Australia, and Japan.

Based on this information we have considered, a balancing of the four evaluation criteria weighs in favor of melatonin for oral administration being added to the 503A Bulks List.

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APPENDIX 1: Melatonin Efficacy For Treatment Of Insomnia And Primary Sleep Disorders

FDA's evaluation of melatonin's effectiveness was based on information regarding the use of melatonin to treat sleep disorders in children and adolescents with autism spectrum disorder. The discussions of the use of melatonin in the other pediatric populations and in certain adult populations are included below in this section as background information. However, the other uses were not considered for the overall assessment and recommendation.

Insomnia in Adults and Approved Treatments

Insomnia is more common in women than in men, and its prevalence is increased in persons who work irregular shifts and in persons with disabilities (Roth et al. 2011). Difficulty maintaining sleep is the most common symptom (affecting 61% of persons with insomnia), followed by early-morning awakening (52%) and difficulty falling asleep (38%); nearly half of those with insomnia have two or more of these symptoms (Walsh et al. 2011). Prolonged sleeplessness is often associated with substantial distress, impairment in daytime functioning, or both.

Marketed prescription insomnia drugs indicated in adults are listed below, and the prescribing information can be accessed by searching Drugs@FDA. The URL for the referenced FDA webpage accessed on March 01, 2021 can be found at https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information.

Ambien (zolpidem)
Belsomra (suvorexant)
Butisol (butabarbital)
Doral (quazepam)
Edluar (zolpidem)
Estazolam
Flurazepam
Halcion (triazolam)
Hetlioz (tasimelteon)
Intermezzo (zolpidem)
Lunesta (eszopiclone)
Restoril (temazepam)
Rozerem (ramelteon)
Seconal (secobarbital)
Silenor (doxepin)
Sonata (zaleplon)
Zolpimist (zolpidem)

Marketed nonprescription insomnia drugs include:
Benadryl (diphenhydramine)*
Unisom (doxylamine)*
*Also in many cold and headache combination products

Ramelteon (Rozerem) is a synthetic melatonin receptor agonist and is indicated for the treatment of insomnia. Schedule IV controlled substances[38] include the benzodiazepine sedatives such as triazolam (Halcion), estazolam, temazepam (Restoril), flurazepam, and quazepam (Doral) and non-benzodiazepine sedatives such as zolpidem (Ambien, Edluar, Intermezzo, Zolpimist), eszopiclone (Lunesta), and zaleplon (Sonata) are drugs that can help induce sleep. However, these medicines may be addictive with extended use. They may also be dangerous if you take them with alcohol or other drugs that depress the central nervous system. They can cause morning sleepiness, although side effects are generally less severe with the non-benzodiazepines. Butabarbital is a Schedule III controlled substance. Secobarbital is a Schedule II controlled substance.

Belsomra (suvorexant) is the first approved orexin receptor antagonist. Orexins are chemicals that are involved in regulating the sleep-wake cycle and play a role in keeping people awake. Doxepin (Silenor) is approved for treating people who have trouble staying asleep. Silenor may help with sleep maintenance by blocking histamine receptors. Patients should not take Silenor unless they are able to get a full seven or eight hours of sleep.

Melatonin for the Treatment of Primary Sleep Disorders in Adults and Children

A systematic review of the literature in the PubMed database was searched for randomized, placebo-controlled trials ***examining the effects of melatonin for the treatment of primary sleep disorders*** in adults and children (Ferracioli-Oda et al. 2013). Primary outcomes examined were improvement in sleep latency, sleep quality and total sleep time. Meta-regression was performed to examine the influence of dose and duration of melatonin on reported efficacy.

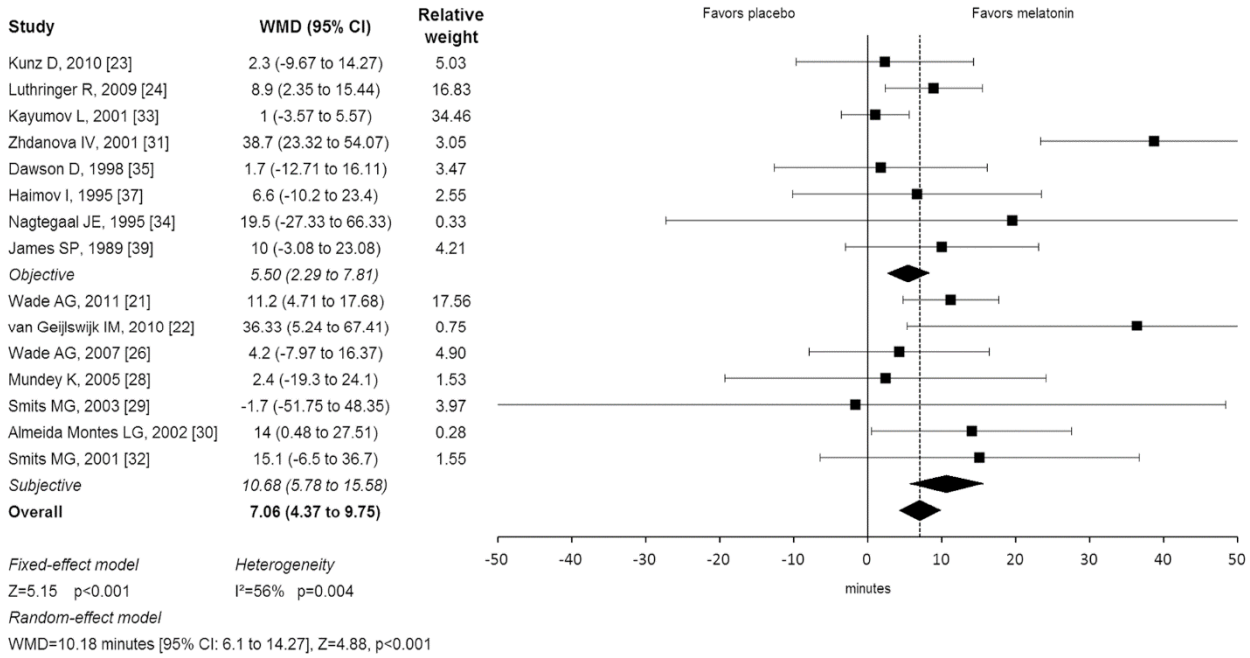
Nineteen studies involving 1683 subjects were included in this meta-analysis. Trials were included if they (1) analyzed primary sleep disorders as defined by the DSM-IV, (2) examined the effects of melatonin, (3) were randomized placebo controlled trials, (4) had at least 10 participants for parallel designs or 5 participants for crossover designs and (5) were published in English.[39]

The forest plot in Figure 14 shows that compared to placebo treated subjects, melatonin reduced sleep latency (weighted mean difference (WMD) = 7.06 minutes [95% CI 4.37 to 9.75]), i.e., on average with melatonin treatment subjects fell asleep 7 minutes earlier on average than subjects receiving placebo.

[38] Information on the United States Drug Enforcement Administration's (DEA's) drug schedules can be found at https://www.dea.gov/drug-scheduling. As stated on DEA's website, drugs, substances, and certain chemicals used to make drugs are classified into 5 distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs have a high potential for abuse and the potential to create severe psychological and/or physical dependence.

[39] Details of the characteristics of the individual studies including the doses and duration may be accessed at DOI: 10.1371/journal.pone.0063773.

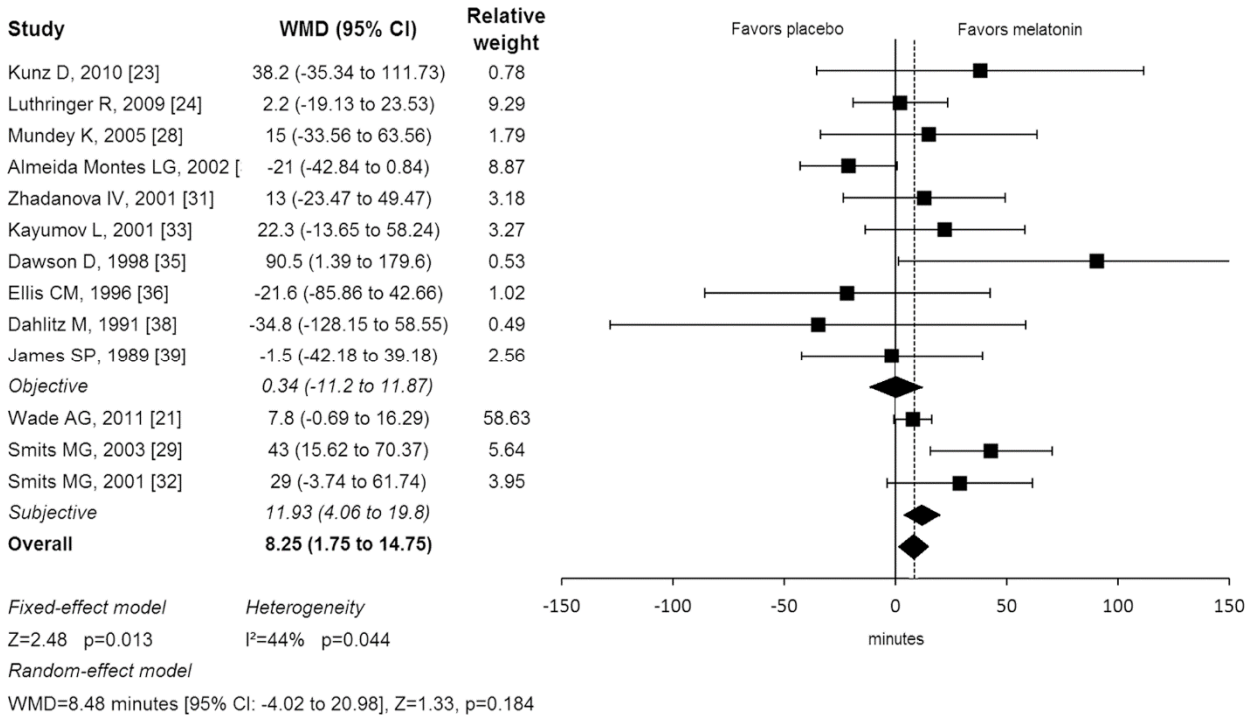
Figure 14: Efficacy of Melatonin in Reducing Sleep Latency (Ferracioli-Oda et al. 2013)



WMD=weighted mean difference; CI=confidence interval.

The forest plot in Figure 15 show that compared to placebo treated subjects, melatonin increased total sleep time (WMD = 8.25 minutes [95% CI 1.74 to 14.75]) i.e., on average with melatonin treatment subjects slept 8 minutes longer on average than subjects receiving placebo. Trials with longer duration and using higher doses of melatonin demonstrated greater effects on decreasing sleep latency and increasing total sleep time. Overall sleep quality was improved in subjects taking melatonin compared to placebo.

Figure 15: Efficacy of Melatonin in Increasing Total sleep Time (Ferracioli-Oda et al. 2013)



The study authors concluded that the effects of melatonin on sleep are modest. Although the absolute benefit of melatonin compared to placebo is smaller than other pharmacological treatments for insomnia, melatonin may have a role in the treatment of insomnia given its benign AE profile compared to the marketed treatments for insomnia.

The 2004 evidence-based review conducted by the Agency for Healthcare Research and Quality (AHRQ) found that melatonin supplements, which are often used for problems sleeping, appeared to be safe when used over a period of days or weeks for most secondary sleep disorders, at relatively high doses and in various formulations (Buscemi et al. 2004). For most sleep disorders the authors found limited support or no benefits of melatonin supplements.

The American Academy of Sleep Medicine practice guideline for the pharmacologic treatment of chronic insomnia in adults recommended that clinicians not use melatonin[40] as a treatment for

[40] It should be noted that use of eight different pharmacological agents for treatment of chronic insomnia in adults were recommended and use of six (including melatonin) were not recommended. All 14 recommendations in this Practice Guideline were graded as "WEAK". The publication stated: "Under GRADE, a STRONG recommendation is one that clinicians should, under most circumstances, follow. A WEAK recommendation reflects a lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients, but should not be construed as an indication of ineffectiveness. GRADE recommendation strengths do not refer to the magnitude of treatment effects in a particular patient, but rather, to the strength of evidence in published data. Downgrading the quality of evidence for these treatments is predictable in GRADE, due to the funding source for most pharmacological clinical trials and the attendant risk of publication bias; the relatively small number of eligible trials for each individual agent; and the observed heterogeneity in the data. The ultimate judgment regarding propriety of any specific care must be made by the clinician in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources."

sleep onset or sleep maintenance insomnia (versus no treatment) in adults (Sateia et al. 2017). In addition, the American College of Physicians clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults had similar interpretations based on their review of electronic databases (2004 – 2015) and stated that there was insufficient or low strength of evidence for melatonin use as sedative hypnotics. Evidence on global and sleep outcomes was insufficient, although effect sizes were small. (Wilt et al. 2016).

Melatonin for the prevention or treatment of jet lag in adults

Jet lag is a common complaint of travelers who fly across a number of time zones. Symptoms of jet lag are primarily daytime fatigue and sleep disturbance, but also include loss of mental efficiency, weakness and irritability (Herxheimer and Petrie 2002). The Cochrane systematic review of oral melatonin for the prevention and treatment of jet lag concluded that eight of the ten trials found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5 mg were similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg. Doses above 5 mg appear to be no more effective. The relative ineffectiveness of 2 mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time.

The authors concluded that the incidence of other side effects is low and occasional short-term use by adults appears to be safe. There may be potential interaction of melatonin in patients using vitamin K antagonists like warfarin or another oral anticoagulant and possible effects of melatonin on seizure activity because of cases reports in addition to reports of fixed drug eruption, an allergic manifestation (Herxheimer and Petrie 2002).

Of note, Section I. Introduction, section of this review discussed melatonin 1 mg/ml oral solution (Colonis Pharma Ltd) that was approved in the UK in 2019 for the short-term (up to 5 days) treatment of jetlag in adults.

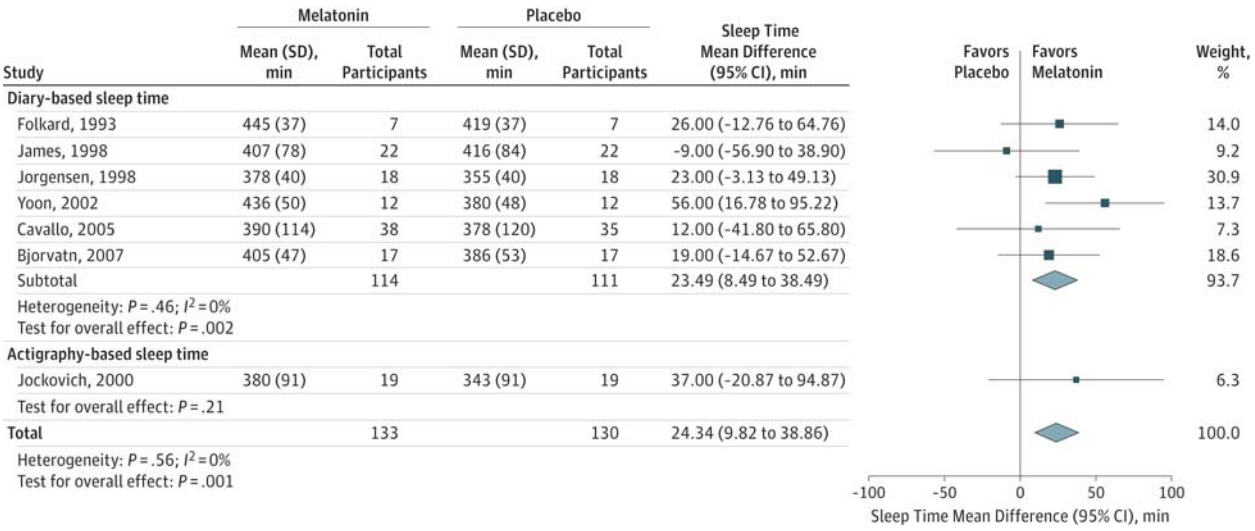
Melatonin in adults with sleepiness and sleep disturbances caused by shift work

In the United States, 29% of workers do not work regular daytime shifts. Shiftwork is associated with reduced sleep duration, impaired daytime sleep quality, and reduced alertness during night shifts. Workers frequently use pharmacological products to ameliorate the adverse effects of shiftwork (Liira et al. 2014).

The Cochrane systematic review of pharmacological interventions for sleepiness and sleep disturbances caused by shift work included nine trials evaluating the effect of melatonin for these uses. The main results were that people who take melatonin (1 to 10 mg) after the night shift may sleep for 24 minutes longer (total sleep time) during the daytime after the night shift and there may be no effect on other sleep outcomes, such as time needed to fall asleep (Figure 16). There was no dose-response effect on sleep. Adverse events reported with melatonin use were rare. The author's conclusions were: 1) there is low quality evidence that melatonin improves sleep length after a night shift, but not other sleep quality parameters, 2) we need more and better

quality trials on the beneficial and adverse effects and costs of all pharmacological agents that induce sleep or promote alertness in shift workers both with and without a diagnosis of shift work sleep disorder, and 3) we also need systematic reviews of their adverse effects (Liira et al. 2014).

Figure 16: The Association of Melatonin With Self-Reported and Objectively Measured Sleep Duration During Days After the Night Shift (Liira et al. 2015)



Study	Melatonin Mean (SD), min	Melatonin Total Participants	Placebo Mean (SD), min	Placebo Total Participants	Sleep Time Mean Difference (95% CI), min	Weight, %
Diary-based sleep time						
Folkard, 1993	445 (37)	7	419 (37)	7	26.00 (-12.76 to 64.76)	14.0
James, 1998	407 (78)	22	416 (84)	22	-9.00 (-56.90 to 38.90)	9.2
Jorgensen, 1998	378 (40)	18	355 (40)	18	23.00 (-3.13 to 49.13)	30.9
Yoon, 2002	436 (50)	12	380 (48)	12	56.00 (16.78 to 95.22)	13.7
Cavallo, 2005	390 (114)	38	378 (120)	35	12.00 (-41.80 to 65.80)	7.3
Bjorvatn, 2007	405 (47)	17	386 (53)	17	19.00 (-14.67 to 52.67)	18.6
Subtotal		114		111	23.49 (8.49 to 38.49)	93.7
Heterogeneity: $P = .46$; $I^2 = 0\%$ Test for overall effect: $P = .002$						
Actigraphy-based sleep time						
Jockovich, 2000	380 (91)	19	343 (91)	19	37.00 (-20.87 to 94.87)	6.3
Test for overall effect: $P = .21$						
Total		133		130	24.34 (9.82 to 38.86)	100.0
Heterogeneity: $P = .56$; $I^2 = 0\%$ Test for overall effect: $P = .001$						

Melatonin to promote sleep in adults in the intensive care unit

The Cochrane systematic review of melatonin for promoting sleep in adults (over the age of 16) admitted to the ICU with any diagnoses included four studies with 151 randomized participants. Two studies included participants who were mechanically ventilated, one study included a mix of ventilated and non-ventilated participants and in one study participants were being weaned from mechanical ventilation.

The effects of melatonin on subjectively reported quantity and quality of sleep were measured through reports of participants or family members or by nursing personnel assessments. There was no difference in sleep scores measured between treated groups and no difference in duration of sleep observed by nurses. Similar observations were reported using objective assessments measured by polysomnography, actigraphy or electroencephalogram. The authors concluded that there was insufficient evidence to determine whether administration of melatonin would improve the quality and quantity of sleep in ICU patients (Lewis et al. 2018).

Tab 2

Methylcobalamin

Tab 2a

Methylcobalamin Nominations

Alliance for Natural Health USA
6931 Arlington Road, Suite 304
Bethesda, MD 20814

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
anhinternational.org

September 30, 2014

VIA ELECTRONIC SUBMISSION

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: "Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations" published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the "Agency").

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the "503A List"). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

As discussed in detail below, in the interest compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA's members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA's Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp.,[1] with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

[1] As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylcobalamin, Mecobalamin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylcobalamin on Pubmed. Key word: methylcobalamin. Please see section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=methylcobalamin
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for methylcobalamin, mecobalamin
Were any monographs for the ingredient found in the USP or NF monographs?	Not for methylcobalamin, mecobalamin
What is the chemical name of the substance?	Methylcobalamin
What is the common name of the substance?	Mecobalamin, MeB12, Methyl Vitamin B12, Methyl B12, McCbl, Methycobal, Methylcobaz
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	JP
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylcobalamin is supplies as dark red crystals or crystalline powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP monograph available EU monograph available EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 236-535-3). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	1. 1 mg/mL MDV (1,000 mcg/mL; 30 mg/mL) 2. 10 mg/mL MDV (10,000 mcg/mL; 100 mg/10 mL; 300 mg/30mL) 3. 20 mg/mL PFV (20,000 mcg/mL; 20 mg/mL)
What are the anticipated route(s) of administration of the compounded drug product(s)?	Intramuscular, Intravenous,Subcutaneous

Are there safety and efficacy data on compounded drugs using the nominated substance?	glutathione redox status. Autism Res Treat. 2013;2013 2. Xu G. et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94 3. Chiu CK, et al. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011 Dec;52(12):868-73. 4. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find exp clin Pharmacol 1995;17:539-544 5. W. Friedrich, Ed. (de Gruyter, Berlin, 1988). Review: "Vitamin B12" in Vitamins. pp 837-928. 6. Mitsuyama Y., Kogoh H. Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment – preliminary study. Jpn J Psychiatry Neurol. 1988 Mar;42(1):65-71. 7. Okuda K., Yashima K., Kitazaki T., Takara I. Intestinal absorption and concurrent chemical changes of Methylcobalamin. J. Lab Clin Med 1973;81:557-567. 8. Are you getting enough of this vitamin? Harv Health Lett. 2005;30(10):1-2.[PubMed 16206385] 9. 2. Beck WS. Cobalamin as coenzyme: A twisting trail of research. Am J Hematol. 1990;34(2):83-89.[PubMed 2187340] Muscle Nerve Journal December 1998 Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study. Kaji R, Kodama M, Imamura A, Hashida T, Kohara N, Ishizu M, Inui K, Kimura J. Department of Neurology, Kyoto University School of Medicine, Japan. Abstract
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	1. Vitamin B12 deficiency in patients with methylation issues, GI disorders, lack of intrinsic factor. 2. A treatment for Austism Syndrome Disorder with Methylations issues. 3. Fibromyalgia, Chronic fatigue syndrome, neuropathic pain. Methylcobalamin is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves. Methionine is required for the metabolism of choline and betaine. This helps explain some of the neurological damage caused by B12 deficiency. The main uses of all forms of B12 are for B12 deficiency, resulting in conditions such as pernicious anemia.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	FDA-approved B12 products are: Cyanocobalamin, & Hydroxocobalamin. Cyanocobalamin is best used IM. Not recommended to give IV due to most vitamins being lost in urine. Hydroxocobalamin, a more long acting B12, binds to serum proteins better than Cyanocobalamin. Hydroxocobalamin is also used as a treatment for cyanide poisoning. Methylcobalamin is a metabolically active form of B12 especially suited for neurological complaints. If there is a particular patient population that would benefit from the use of methylcobalamin because of neurological deficits, methylcobalamin would benefit this patient population more than cyanocobalamin or hydroxyocobalamin.

Is there any other relevant information?	11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746] 13. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448-457.[PubMed 20882439] 14. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24-27.[PubMed 19904199] 15. McCaddon A, Hudson PR. L-methylfolate, methylcobalamin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. CNS Spectr. 2010;15(1 Suppl 1):2-5; discussion 6.[PubMed 20397369] 16. Pepper MR, Black MM. B12 in fetal development. Semin Cell Dev Biol. 2011;22(6):619-623.[PubMed 21664980] 17. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev. 2006;11(4):294-329.[PubMed 17176168] 18. Maladkar M, Rajadhyaksha G, Venkataswamy N, et al. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. Int J Diabetes Dev Ctries. 2009;29(1):28-34.[PubMed 20062561] 19. Sharma V, Biswas D. Cobalamin deficiency presenting as obsessive compulsive disorder: Case report. Gen Hosp Psychiatry. 2012.[PubMed 22227032] 20. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662-668.[PubMed 20717016] 21. Rafnsson SB, Saravanan P, Bhopal RS, Yajnik CS. Is a low blood level of vitamin B12 a cardiovascular and diabetes risk factor? A systematic review of cohort studies. Eur J Nutr. 2011;50(2):97-106.[PubMed 20585951] 22. Pezzini A, Del Zotto E, Padovani A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem. 2007;14(3):249-263.[PubMed 17305530] 23. Wheatley C. Cobalamin in inflammation III - glutathionylcobalamin and methylcobalamin/adenosylcobalamin coenzymes: The sword in the stone? how cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 2007;16(3-4):212-226.[PubMed 18923642] 24. Guttuso T Jr, McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, "Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances" relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and

doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency's request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

Naturopathic Medicine and Naturopathic Physicians

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient's condition rather than focusing solely on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses, and order lab tests, imaging procedures, and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate.

NDs attend 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 such schools in North America. Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.

Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors, as well as compounding pharmacists, to ensure safe and comprehensive care.

Characteristics of Patients Seen by Naturopathic Physicians

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors' offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients' immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the 'multi-systems' approach of naturopathic medicine – of which compounded drugs are an essential component.

Bulk Drug Substances Nominated at this Time

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency's criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine

Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium L5 Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutiathone
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene

Pyridoxal 5-Phosphate
Resveratrol
Salicinium
Thymol Iodide

AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA's approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act") – particularly for drugs that have been safely used for years, not only with the Agency's implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals. The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA's complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients' clinical outcomes than provided a bona fide contribution to patient safety.

Conclusion

AANP appreciates the Agency's consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylcobalamin, Mecobalamin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylcobalamin on Pubmed. Key word: methylcobalamin. Please see section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=methylcobalamin
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for methylcobalamin, mecobalamin
Were any monographs for the ingredient found in the USP or NF monographs?	Not for methylcobalamin, mecobalamin
What is the chemical name of the substance?	Methylcobalamin
What is the common name of the substance?	Mecobalamin, MeB12, Methyl Vitamin B12, Methyl B12, McCbl, Methycobal, Methylcobaz
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	JP
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylcobalamin is supplies as dark red crystals or crystalline powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP monograph available EU monograph available EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 236-535-3). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	1. 1 mg/mL MDV (1,000 mcg/mL; 30 mg/mL) 2. 10 mg/mL MDV (10,000 mcg/mL; 100 mg/10 mL; 300 mg/30mL) 3. 20 mg/mL PFV (20,000 mcg/mL; 20 mg/mL)
What are the anticipated route(s) of administration of the compounded drug product(s)?	Intramuscular, Intravenous,Subcutaneous

Are there safety and efficacy data on compounded drugs using the nominated substance?	glutathione redox status. Autism Res Treat. 2013;2013 2. Xu G. et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94 3. Chiu CK, et al. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011 Dec;52(12):868-73. 4. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find exp clin Pharmacol 1995;17:539-544 5. W. Friedrich, Ed. (de Gruyter, Berlin, 1988). Review: "Vitamin B12" in Vitamins. pp 837-928. 6. Mitsuyama Y., Kogoh H. Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment – preliminary study. Jpn J Psychiatry Neurol. 1988 Mar;42(1):65-71. 7. Okuda K., Yashima K., Kitazaki T., Takara I. Intestinal absorption and concurrent chemical changes of Methylcobalamin. J. Lab Clin Med 1973;81:557-567. 8. Are you getting enough of this vitamin? Harv Health Lett. 2005;30(10):1-2.[PubMed 16206385] 9. 2. Beck WS. Cobalamin as coenzyme: A twisting trail of research. Am J Hematol. 1990;34(2):83-89.[PubMed 2187340] Muscle Nerve Journal December 1998 Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study. Kaji R, Kodama M, Imamura A, Hashida T, Kohara N, Ishizu M, Inui K, Kimura J. Department of Neurology, Kyoto University School of Medicine, Japan. Abstract
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	1. Vitamin B12 deficiency in patients with methylation issues, GI disorders, lack of intrinsic factor. 2. A treatment for Austism Syndrome Disorder with Methylations issues. 3. Fibromyalgia, Chronic fatigue syndrome, neuropathic pain. Methylcobalamin is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves. Methionine is required for the metabolism of choline and betaine. This helps explain some of the neurological damage caused by B12 deficiency. The main uses of all forms of B12 are for B12 deficiency, resulting in conditions such as pernicious anemia.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	FDA-approved B12 products are: Cyanocobalamin, & Hydroxocobalamin. Cyanocobalamin is best used IM. Not recommended to give IV due to most vitamins being lost in urine. Hydroxocobalamin, a more long acting B12, binds to serum proteins better than Cyanocobalamin. Hydroxocobalamin is also used as a treatment for cyanide poisoning. Methylcobalamin is a metabolically active form of B12 especially suited for neurological complaints. If there is a particular patient population that would benefit from the use of methylcobalamin because of neurological deficits, methylcobalamin would benefit this patient population more than cyanocobalamin or hydroxyocobalamin.

Is there any other relevant information?	11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746] 13. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448-457.[PubMed 20882439] 14. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24-27.[PubMed 19904199] 15. McCaddon A, Hudson PR. L-methylfolate, methylcobalamin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. CNS Spectr. 2010;15(1 Suppl 1):2-5; discussion 6.[PubMed 20397369] 16. Pepper MR, Black MM. B12 in fetal development. Semin Cell Dev Biol. 2011;22(6):619-623.[PubMed 21664980] 17. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev. 2006;11(4):294-329.[PubMed 17176168] 18. Maladkar M, Rajadhyaksha G, Venkataswamy N, et al. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. Int J Diabetes Dev Ctries. 2009;29(1):28-34.[PubMed 20062561] 19. Sharma V, Biswas D. Cobalamin deficiency presenting as obsessive compulsive disorder: Case report. Gen Hosp Psychiatry. 2012.[PubMed 22227032] 20. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662-668.[PubMed 20717016] 21. Rafnsson SB, Saravanan P, Bhopal RS, Yajnik CS. Is a low blood level of vitamin B12 a cardiovascular and diabetes risk factor? A systematic review of cohort studies. Eur J Nutr. 2011;50(2):97-106.[PubMed 20585951] 22. Pezzini A, Del Zotto E, Padovani A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem. 2007;14(3):249-263.[PubMed 17305530] 23. Wheatley C. Cobalamin in inflammation III - glutathionylcobalamin and methylcobalamin/adenosylcobalamin coenzymes: The sword in the stone? how cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 2007;16(3-4):212-226.[PubMed 18923642] 24. Guttuso T Jr, McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial.

ACAM
American College for Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to compound Drug Products in Accordance With Section 503B of Federal Food, Drug, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in instructing physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. We have a strong interest in maintaining the availability of compounded drug products.

We appreciate the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information. In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503B.

ACAM
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380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylcobalamin, Mecobalamin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylcobalamin on Pubmed. Key word: methylcobalamin. Please see section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=methylcobalamin
What is the chemical name of the substance?	Methylcobalamin
What is the common name of the substance?	Mecobalamin, MeB12, Methyl Vitamin B12, Methyl B12, McCbl, Methycobal, Methylcobaz
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	JP
What is the strength, quality, stability, and purity of the ingredient?	Methylcobalamin, JP Methylcobalamin, EU A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylcobalamin is supplies as dark red crystals or crystalline powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP monograph available EU monograph available EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 236-535-3). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	1. Vitamin B12 deficiency in patients with methylation issues, GI disorders, lack of intrinsic factor 2. A treatment for Austism Syndrome Disorder with Methylations issues. 3. Fibromyalgia, Chronic fatigue syndrome, neuropathic pain, multiple sclerosis, parkinsonism, etc. Methylcobalamin is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves. Methionine is required for the metabolism of choline and betaine. This helps explain some of the neurological damage caused by B12 deficiency. The main uses of all forms of B12 are for B12 deficiency, resulting in conditions such as pernicious anemia.

Are there other drug products approved by FDA to treat the same medical condition?	FDA-approved B12 products are: Cyanocobalamin, Hydroxocobalamin. Cyanocobalamin is best used IM as much of the dose is lost as blood circulates through the kidneys. Hydroxocobalamin, a more long acting B12, binds to serum proteins better than Cyanocobalamin. Hydroxocobalamin is also used as a treatment for cyanide poisoning. Methylcobalamin is a metabolically active form of B12 especially suited for neurological complaints. If there is a particular patient population that would benefit from the use of methylcobalamin because of neurological deficits, methylcobalamin would benefit this patient population more than cyanocobalamin or hydroxyocobalamin.
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product? Provide a justification for clinical need, including an estimate of the size of the population that would need the compounded drug.	1. risperidone and aripiprazole are not FDA-approved to treat Austistic Syndrome Disorder itself, only irritability associated with Autism. Risperidone and aripiprazole have a significant boxed warning and profile of CNS side effects in long-term use. 2. duloxetine has a significant boxed warning, SEs and drug interaction profile. **Thousands** of patients with methylation issues, autistism, chronic fatigue, fibromyalgia, multiples sclerosis, parkinsonism, neuropathy, autoimmune, and heavy metal toxic syndrome are prescribed and use methylcobalamin daily. Our mothers, sisters and brothers are taking methylcobalamin to control their neuropathic conditions.
Are there safety and efficacy data on compounded drugs using the nominated substance?	glutathione redox status. Autism Res Treat. 2013;2013 2. Xu G. et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94 3. Chiu CK, et al. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011 Dec;52(12):868-73. 4. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find exp clin Pharmacol 1995;17:539-544 5. W. Friedrich, Ed. (de Gruyter, Berlin, 1988). Review: "Vitamin B12" in Vitamins. pp 837-928. 6. Mitsuyama Y., Kogoh H. Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment – preliminary study. Jpn J Psychiatry Neurol. 1988 Mar;42(1):65-71. 7. Okuda K., Yashima K., Kitazaki T., Takara I. Intestinal absorption and concurrent chemical changes of Methylcobalamin. J. Lab Clin Med 1973;81:557-567. 8. Are you getting enough of this vitamin? Harv Health Lett. 2005;30(10):1-2.[PubMed 16206385] 9. 2. Beck WS. Cobalamin as coenzyme: A twisting trail of research. Am J Hematol. 1990;34(2):83-89.[PubMed 2187340] 0. Olson RE. Karl August Folkers (1906-1997). J Nutr. 2001;131(9):2227-2230.[PubMed 11533258] 11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746]
If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	There is no FDA-approved drug product including methylcobalamin
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	1. 1 mg/mL MDV (1,000 mcg/mL; 30 mg/mL) 2. 10 mg/mL MDV (10,000 mcg/mL; 100 mg/10 mL; 300 mg/30mL) 3. 20 mg/mL PFV (20,000 mcg/mL; 20 mg/mL)
What are the anticipated route(s) of administration of the compounded drug product(s)?	I.M. or S.Q.
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
Is there any other relevant information?	**There is a manufactured product in Japan called Methylco injection 500 mcg/mL.** 10. Olson RE. Karl August Folkers (1906-1997). J Nutr. 2001;131(9):2227-2230.[PubMed 11533258] 11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746] 13. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448-457.[PubMed 20882439] 14. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24-27.[PubMed 19904199] 15. McCaddon A, Hudson PR. L-methylfolate, methylcobalamin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. CNS Spectr. 2010;15(1 Suppl 1):2-5; discussion 6.[PubMed 20397369] 16. Pepper MR, Black MM. B12 in fetal development. Semin Cell Dev Biol. 2011;22(6):619-623.[PubMed 21664980] 17. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev. 2006;11(4):294-329.[PubMed 17176168] 18. Maladkar M, Rajadhyaksha G, Venkataswamy N, et al. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. Int J Diabetes Dev Ctries. 2009;29(1):28-34.[PubMed 20062561] 19. Sharma V, Biswas D. Cobalamin deficiency presenting as obsessive compulsive disorder: Case report. Gen Hosp Psychiatry. 2012.[PubMed 22227032] 20. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662-668.[PubMed 20717016] 21. Rafnsson SB, Saravanan P, Bhopal RS, Yajnik CS. Is a low blood level of vitamin B12 a cardiovascular and diabetes risk factor? A systematic review of cohort studies. Eur J Nutr. 2011;50(2):97-106.[PubMed 20585951] 22. Pezzini A, Del Zotto E, Padovani A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem. 2007;14(3):249-263.[PubMed 17305530] 23. Wheatley C. Cobalamin in inflammation III - glutathionylcobalamin and methylcobalamin/adenosylcobalamin coenzymes: The sword in the stone? how cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 2007;16(3-4):212-226.[PubMed 18923642] 24. Guttuso T Jr, McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial. Menopause. 2009;16(5):1004-1008.[PubMed 19407666] 25. Zoccolella S, Bendotti C, Beghi E, Logroscino G. Homocysteine levels and amyotrophic lateral sclerosis: A possible link. Amyotroph Lateral Scler. 2010;11(1-2):140-147.[PubMed 19551535] 26. Tanaka N, Yamazaki Y, Yamada H et al. Fate of cobalamins in humans following oral and intramuscular administration of cyanocobalamin, hydroxycobalamin, adenosylcobalamin and methylcobalamin. Vitamins. 1981;55:155–161. 27. Methylcobalamin. In: Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 9th ed. Philadelphia, PA: Wolters Kluwer Health Inc/Lippincott Williams & Wilkins; 2011. 28. Vitamin B12 Substances. In: Sweetman SC, ed. Martindale: The Complete Drug Reference. 37th ed. London, England: Pharmaceutical Press; 2011. 29. Bistrian B. Should I stop taking these vitamins? Harv Health Lett. 2010;35(7):2.[PubMed 20583349] 30. European Commission. Opinion of the scientific committee on food on the tolerable upper intake level of vitamin B12. 2000;SCF/CS/NUT/UPPLEV/42 Final. http://ec.europa.eu.ezproxy.auckland.ac.nz/food/fs/sc/scf/out80d_en.pdf. Accessed May 2012.

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act"

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs

Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlxs file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 –D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

Fagron - 2400 Pilot Knob Road - St. Paul, MN 55120 - Tel. (800) 423 6967 - Fax (800) 339 1596

Fagron

2400 Pilot Knob Road
St. Paul, Minnesota 55120 - USA
(800) 423 6967
www.fagron.us

What is the name of the nominated ingredient?	**Methylcobalamin**
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Yes, Methylcobalamin is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect. References for Methylcobalamin pharmacological actions are provided Prabhoo R, Panghate A, Dewda RP, More B, Prabhoo T, Rana R. Efficacy and tolerability of a fixed dose combination of methylcobalamin and pregabalin in the management of painful neuropathy. N Am J Med Sci. 2012 Nov;4(11):605-7. http://www.ncbi.nlm.nih.gov/pubmed/23181238 Xu G, Lv ZW, Feng Y, Tang WZ, Xu GX. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94. http://www.ncbi.nlm.nih.gov/pubmed/23566267 Chiu CK, Low TH, Tey YS, Singh VA, Shong HK. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011. http://www.ncbi.nlm.nih.gov/pubmed/22159928 Koyama K, Usami T, Takeuchi O, Morozumi K, Kimura G. Efficacy of methylcobalamin on lowering total
Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/ scripts/cder/ob/docs/queryai.cfm. The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com. The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	Coα-[α-(5,6-dimethyl-1H-benzoimidazol-1-yl)]-Coβmethylcobamide
What is the common name of the substance?	Methylcobalamin; Mecobalamin; Mecobalamina; Mecobalaminum; Coα-[α-(5,6-dimethylbenz-1H-imidazolyl)]-Coβmethylcobamide; MeB12
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	no grade

What is the strength, quality, stability, and purity of the ingredient?	Description: Dark red crystals or crystalline powder Identification UV: Compare the spectrum with reference spectrum, both spectra exhibit similar intensities of absorption at the same wavelengths Chemical: Meets JP requirements Clarity of Solution: Solution is clear and red color Total Content: ≤ 2.0% Max Related Substances: ≤ 0.5% Assay (Dried): ≥ 98.0% Water: ≤ 12.0% Lead: ≤ 1 ppm Mercury: ≤ 1 ppm Arsenic: ≤ 5 ppm Cadmium: ≤ 1 ppm Residual Solvents: Acetone: ≤ 1000 ppm - Ethanol: ≤ 1000 ppm Total Plate Count: ≤ 1000 cfu/g Yeast and Mold: ≤ 100 cfu/g E. Coli: Negative Salmonella: Negative
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP (Japanese Pharmacopoeia XVI, 2011, page 1066)
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Troche
What strength(s) will be compounded from the nominated substance?	5-20mg
What are the anticipated route(s) of administration of the compounded drug product(s)?	Sublingual

Are there safety and efficacy data on compounded drugs using the nominated substance?	Frye RE, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters L, James SJ. Effectiveness of methylcobalamin and folinic Acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. Autism Res Treat. 2013;2013:609705. http://www.ncbi.nlm.nih.gov/pubmed/24224089 Prabhoo R, Panghate A, Dewda RP, More B, Prabhoo T, Rana R. Efficacy and tolerability of a fixed dose combination of methylcobalamin and pregabalin in the management of painful neuropathy. N Am J Med Sci. 2012 Nov;4(11):605-7. http://www.ncbi.nlm.nih.gov/pubmed/23181238 Xu G, Lv ZW, Feng Y, Tang WZ, Xu GX. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94. http://www.ncbi.nlm.nih.gov/pubmed/23566267 Chiu CK, Low TH, Tey YS, Singh VA, Shong HK. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011. http://www.ncbi.nlm.nih.gov/pubmed/22159928 Koyama K, Usami T, Takeuchi O, Morozumi K, Kimura G. Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation. Nephrol Dial Transplant. 2002 May;17(5):916-22. http://www.ncbi.nlm.nih.gov/pubmed/11981084 Kim HI, Hyung WJ, Song KJ, Choi SH, Kim CB, Noh SH. Oral vitamin B12 replacement: an effective treatment for vitamin B12 deficiency after total gastrectomy in gastric cancer patients. Ann Surg Oncol. 2011 Dec;18(13):3711-7. http://www.ncbi.nlm.nih.gov/pubmed/21556950 Ikeda T, Yamamoto K, Takahashi K, Kaku Y, Uchiyama M, Sugiyama K, Yamada M. Treatment of Alzheimer-type dementia with intravenous mecobalamin. Clin Ther. 1992 May-Jun;14(3):426-37. http://www.ncbi.nlm.nih.gov/pubmed/1638584 Dongre YU, Swami OC. Sustained-release pregabalin with methylcobalamin in neuropathic pain: an Indian real-life experience. Int J Gen Med. 2013 May 29;6:413-7.
Has the bulk drug substance been used previously to compound drug product(s)?	Yes, Methylcobabalamin has been compounded for the treatment of neuropathic disorders, paresthesia, Autism, pernicious animia, hyperhomocysteinimia and chronic fatigue.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Autism, diabetic neuropathy, vitamin B12 nutritional supplementation, hyperhomocysteinemia Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. Clin Neurol Neurosurg. 1992;94(2):105-11. http://www.ncbi.nlm.nih.gov/pubmed/1324807

What is the reason for use of a compounded drug product rather than an FDA-approved product?	No FDA approved Methylcobalamin preparation. Dialysis patients have been shown to benefit from Methylcobalamin supplementation. Injectable forms of metylcobalamin used intravenously normalized hyperhomocysteinemia and decreased Asymmetric dimethylargininelevels and arterial stiffness. (K. Koyama, A.Ito,J. Yamamoto,T. Nishio,J. Kajikuri, Y. Dohi, N. Ohte, A. Sano, H. Nakamura, H. Kumagai and T. Itoh(2010) Randomized Controlled Trial of the Effect of Short Term Coadministration of Methyl Cobalamin and Folate on serum ADMA Concentration in Patients Recieving Long Term Hemodialysis Am.J. Kidney Dis Jun;55(6):1069-78) Other FDA options of folate alone are not comparable in efficacy. This same folate combination shows promise in treting redox metabolism abnormalities in Autistic individuals. (R.E. Frye and D.A. Rossignol(2014) Treatments for Biomedical Abnormalities Associated with Autism Spectrum Disorder Front Pediatr Jun27;2:66) It can help with nerve pain transmission with Diabetic neuropathy. (M. Zhang,W, Han,S HU, and H XU (2013) Mathylcobalamin:A Potential Vitamin of Pain killer Neural Plast) Current FDA aproved medications for Diabetic Neurpathy include Gabapentin and Lyrica. They can cause dizziness,drowisness, and interefr with norml cognitive function. Methylcobalamin has less side effects and better safety profile.
Is there any other relevant information?	All relevant information was expressed in the above questions

VIA WWW.REGULATIONS.COM

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations.

To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration's request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food Drug and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the

process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

American Academy of Environmental Medicine (AAEM) www.aaemonline.org
American Association of Naturopathic Physicians (AANP) www.naturopathic.org
American College for Advancement in Medicine (ACAM) www.acam.org
International College of Integrative Medicine (ICIM) www.icimed.com
International Hyperbaric Medical Association (IHMA) www.hyperbaricmedicalassociation.org
International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and subject to Category

I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

IMC Objections and Requests Regarding Docket FDA-2013-N-1525

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA's approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act"), particularly for drugs that have been in use for years, not only with FDA's at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions.

This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the

track record in this industry. This is particularly true given that the infectious contamination that gave rise to the Act has little to do with the approval process for which ingredients may be compounded. Yet FDA has offered little consideration of the respective risks and benefits of its approach, and with pharmacies and physicians carrying the full burden of proof and the time expected for the advisory process to conclude, the FDA will likely itself cause more patient harm than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for "Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness," 79 FR 37687, in which 25 drugs were added to the list of barred drugs, it has not done so for the much broader issue of upending the compounding pharmaceutical industry, which bears costs both in preparation of detailed submissions on potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic consequence to physicians of not being to prescribe these drugs, and the economic impacts of health difficulties and added expense that will result from the withdrawal of drugs from clinical use. The Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC's March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug substances. IMC identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring.[1] We had determined that at least 6 hours per ingredient would be needed to do so, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

[1] For example, other nominations would include 7 Keto Dehydroepiandrosterone; Asparagine; Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin; Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid; Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol Iodide.

day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.

This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use,[2] and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

[2] Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylcobalamin, Mecobalamin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylcobalamin on Pubmed. Key word: methylcobalamin. Please see section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=methylcobalamin
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for methylcobalamin, mecobalamin
Were any monographs for the ingredient found in the USP or NF monographs?	Not for methylcobalamin, mecobalamin
What is the chemical name of the substance?	Methylcobalamin
What is the common name of the substance?	Mecobalamin, MeB12, Methyl Vitamin B12, Methyl B12, McCbl, Methycobal, Methylcobaz
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	JP
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylcobalamin is supplies as dark red crystals or crystalline powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP monograph available EU monograph available EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 236-535-3). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	1. 1 mg/mL MDV (1,000 mcg/mL; 30 mg/mL) 2. 10 mg/mL MDV (10,000 mcg/mL; 100 mg/10 mL; 300 mg/30mL) 3. 20 mg/mL PFV (20,000 mcg/mL; 20 mg/mL)
What are the anticipated route(s) of administration of the compounded drug product(s)?	Intramuscular, Intravenous,Subcutaneous

Are there safety and efficacy data on compounded drugs using the nominated substance?	glutathione redox status. Autism Res Treat. 2013;2013 2. Xu G. et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94 3. Chiu CK, et al. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011 Dec;52(12):868-73. 4. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find exp clin Pharmacol 1995;17:539-544 5. W. Friedrich, Ed. (de Gruyter, Berlin, 1988). Review: "Vitamin B12" in Vitamins. pp 837-928. 6. Mitsuyama Y., Kogoh H. Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment – preliminary study. Jpn J Psychiatry Neurol. 1988 Mar;42(1):65-71. 7. Okuda K., Yashima K., Kitazaki T., Takara I. Intestinal absorption and concurrent chemical changes of Methylcobalamin. J. Lab Clin Med 1973;81:557-567. 8. Are you getting enough of this vitamin? Harv Health Lett. 2005;30(10):1-2.[PubMed 16206385] 9. 2. Beck WS. Cobalamin as coenzyme: A twisting trail of research. Am J Hematol. 1990;34(2):83-89.[PubMed 2187340] Muscle Nerve Journal December 1998 Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study. Kaji R, Kodama M, Imamura A, Hashida T, Kohara N, Ishizu M, Inui K, Kimura J. Department of Neurology, Kyoto University School of Medicine, Japan. Abstract
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	1. Vitamin B12 deficiency in patients with methylation issues, GI disorders, lack of intrinsic factor. 2. A treatment for Austism Syndrome Disorder with Methylations issues. 3. Fibromyalgia, Chronic fatigue syndrome, neuropathic pain. Methylcobalamin is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves. Methionine is required for the metabolism of choline and betaine. This helps explain some of the neurological damage caused by B12 deficiency. The main uses of all forms of B12 are for B12 deficiency, resulting in conditions such as pernicious anemia.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	FDA-approved B12 products are: Cyanocobalamin, & Hydroxocobalamin. Cyanocobalamin is best used IM. Not recommended to give IV due to most vitamins being lost in urine. Hydroxocobalamin, a more long acting B12, binds to serum proteins better than Cyanocobalamin. Hydroxocobalamin is also used as a treatment for cyanide poisoning. Methylcobalamin is a metabolically active form of B12 especially suited for neurological complaints. If there is a particular patient population that would benefit from the use of methylcobalamin because of neurological deficits, methylcobalamin would benefit this patient population more than cyanocobalamin or hydroxyocobalamin.

Is there any other relevant information?	11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746] 13. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448-457.[PubMed 20882439] 14. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24-27.[PubMed 19904199] 15. McCaddon A, Hudson PR. L-methylfolate, methylcobalamin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. CNS Spectr. 2010;15(1 Suppl 1):2-5; discussion 6.[PubMed 20397369] 16. Pepper MR, Black MM. B12 in fetal development. Semin Cell Dev Biol. 2011;22(6):619-623.[PubMed 21664980] 17. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev. 2006;11(4):294-329.[PubMed 17176168] 18. Maladkar M, Rajadhyaksha G, Venkataswamy N, et al. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. Int J Diabetes Dev Ctries. 2009;29(1):28-34.[PubMed 20062561] 19. Sharma V, Biswas D. Cobalamin deficiency presenting as obsessive compulsive disorder: Case report. Gen Hosp Psychiatry. 2012.[PubMed 22227032] 20. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662-668.[PubMed 20717016] 21. Rafnsson SB, Saravanan P, Bhopal RS, Yajnik CS. Is a low blood level of vitamin B12 a cardiovascular and diabetes risk factor? A systematic review of cohort studies. Eur J Nutr. 2011;50(2):97-106.[PubMed 20585951] 22. Pezzini A, Del Zotto E, Padovani A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem. 2007;14(3):249-263.[PubMed 17305530] 23. Wheatley C. Cobalamin in inflammation III - glutathionylcobalamin and methylcobalamin/adenosylcobalamin coenzymes: The sword in the stone? how cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 2007;16(3-4):212-226.[PubMed 18923642] 24. Guttuso T Jr, McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee ***prior*** to the implementation and issuance of regulations including the creation of the bulk ingredient list.

> (2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

> General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Methylcobalamin
Chemical/Common Name	Coalpha-[alpha-(5,6-Dimethylbenzimidazolyl)]-CoBeta-methylcobamide; Mecobalamin
Identifying Codes	13422-55-4
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies *(including foreign recognition)*	JP, Not Listed in USP/NF

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography *(where available)*	
Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension

The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a "deficiency letter" be issued to the person or organization that submitted the nomination? The Agency issues "deficiency letters" for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue "deficiency letters" to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylcobalamin, Mecobalamin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylcobalamin on Pubmed. Key word: methylcobalamin. Please see section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=methylcobalamin
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for methylcobalamin, mecobalamin
Were any monographs for the ingredient found in the USP or NF monographs?	Not for methylcobalamin, mecobalamin
What is the chemical name of the substance?	Methylcobalamin
What is the common name of the substance?	Mecobalamin, MeB12, Methyl Vitamin B12, Methyl B12, McCbl, Methycobal, Methylcobaz
Does the substance have a UNII Code?	BR1SN1JS2W
What is the chemical grade of the substance?	JP
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylcobalamin is supplies as dark red crystals or crystalline powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	JP monograph available EU monograph available EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 236-535-3). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	1. 1 mg/mL MDV (1,000 mcg/mL; 30 mg/mL) 2. 10 mg/mL MDV (10,000 mcg/mL; 100 mg/10 mL; 300 mg/30mL) 3. 20 mg/mL PFV (20,000 mcg/mL; 20 mg/mL)
What are the anticipated route(s) of administration of the compounded drug product(s)?	Intramuscular, Subcutaneous

Are there safety and efficacy data on compounded drugs using the nominated substance?	glutathione redox status. Autism Res Treat. 2013;2013 2. Xu G. et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Pain Med. 2013 Jun;14(6):884-94 3. Chiu CK, et al. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. Singapore Med J. 2011 Dec;52(12):868-73. 4. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find exp clin Pharmacol 1995;17:539-544 5. W. Friedrich, Ed. (de Gruyter, Berlin, 1988). Review: "Vitamin B12" in Vitamins. pp 837-928. 6. Mitsuyama Y., Kogoh H. Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment – preliminary study. Jpn J Psychiatry Neurol. 1988 Mar;42(1):65-71. 7. Okuda K., Yashima K., Kitazaki T., Takara I. Intestinal absorption and concurrent chemical changes of Methylcobalamin. J. Lab Clin Med 1973;81:557-567. 8. Are you getting enough of this vitamin? Harv Health Lett. 2005;30(10):1-2.[PubMed 16206385] 9. 2. Beck WS. Cobalamin as coenzyme: A twisting trail of research. Am J Hematol. 1990;34(2):83-89.[PubMed 2187340] Muscle Nerve Journal December 1998 Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study. Kaji R, Kodama M, Imamura A, Hashida T, Kohara N, Ishizu M, Inui K, Kimura J. Department of Neurology, Kyoto University School of Medicine, Japan. Abstract
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	1. Vitamin B12 deficiency in patients with methylation issues, GI disorders, lack of intrinsic factor. 2. A treatment for Austism Syndrome Disorder with Methylations issues. 3. Fibromyalgia, Chronic fatigue syndrome, neuropathic pain. Methylcobalamin is required to convert homocysteine to methionine and to synthesize and maintain myelin sheaths on nerves. Methionine is required for the metabolism of choline and betaine. This helps explain some of the neurological damage caused by B12 deficiency. The main uses of all forms of B12 are for B12 deficiency, resulting in conditions such as pernicious anemia.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	FDA-approved B12 products are: Cyanocobalamin, & Hydroxocobalamin. Cyanocobalamin is best used IM. Not recommended to give IV due to most vitamins being lost in urine. Hydroxocobalamin, a more long acting B12, binds to serum proteins better than Cyanocobalamin. Hydroxocobalamin is also used as a treatment for cyanide poisoning. Methylcobalamin is a metabolically active form of B12 especially suited for neurological complaints. If there is a particular patient population that would benefit from the use of methylcobalamin because of neurological deficits, methylcobalamin would benefit this patient population more than cyanocobalamin or hydroxyocobalamin.

Is there any other relevant information?	11. Cyanocobalamin (Vitamin B12). Drug Facts & Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2011. Accessed August 14, 2012. 12. Andres E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010;11(2):249-256.[PubMed 20088746] 13. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448-457.[PubMed 20882439] 14. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24-27.[PubMed 19904199] 15. McCaddon A, Hudson PR. L-methylfolate, methylcobalamin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. CNS Spectr. 2010;15(1 Suppl 1):2-5; discussion 6.[PubMed 20397369] 16. Pepper MR, Black MM. B12 in fetal development. Semin Cell Dev Biol. 2011;22(6):619-623.[PubMed 21664980] 17. Head KA. Peripheral neuropathy: Pathogenic mechanisms and alternative therapies. Altern Med Rev. 2006;11(4):294-329.[PubMed 17176168] 18. Maladkar M, Rajadhyaksha G, Venkataswamy N, et al. Efficacy, safety, and tolerability of epalrestat compared to methylcobalamine in patients with diabetic neuropathy. Int J Diabetes Dev Ctries. 2009;29(1):28-34.[PubMed 20062561] 19. Sharma V, Biswas D. Cobalamin deficiency presenting as obsessive compulsive disorder: Case report. Gen Hosp Psychiatry. 2012.[PubMed 22227032] 20. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 2010;13(6):662-668.[PubMed 20717016] 21. Rafnsson SB, Saravanan P, Bhopal RS, Yajnik CS. Is a low blood level of vitamin B12 a cardiovascular and diabetes risk factor? A systematic review of cohort studies. Eur J Nutr. 2011;50(2):97-106.[PubMed 20585951] 22. Pezzini A, Del Zotto E, Padovani A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. Curr Med Chem. 2007;14(3):249-263.[PubMed 17305530] 23. Wheatley C. Cobalamin in inflammation III - glutathionylcobalamin and methylcobalamin/adenosylcobalamin coenzymes: The sword in the stone? how cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 2007;16(3-4):212-226.[PubMed 18923642] 24. Guttuso T Jr, McDermott MP, Ng P, Kieburtz K. Effect of L-methionine on hot flashes in postmenopausal women: a randomized controlled trial.

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
(703) 683-3619 FAX

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Methylcobalamin (Mecobalamin)	co-alpha-[alpha-(5,6-dimethylbenzimidazolyl)]-co-beta-methylcobamide	Carbainde	BR1SN1JS2W	From PCCA Database MSDS: Product is 100% by weight and stable. Should be protected from strong oxidizing agents.	powder	JP, Not USP; sold OTC in US as a dietary supplement.	Capsule, Cream, Solution	Capsules: 1-10mg, Cream: 0.1- 2.5%, Solution: 0.1 - 2.5%	Oral, topical, injectable, nasal spray	James SJ, et al. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009 Jan;89(1):425-30. [http://www.ncbi.nlm.nih.gov/pubmed/19056591] Frye RE, et al. Effectiveness of methylcobalamin and folinic Acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. Autism Res Treat. 2013;2013:609705. [http://www.ncbi.nlm.nih.gov/pubmed/24224089]	Autism Spectrum Disorders, Neurological Disorders, Pain Provides an alternate dosage form and/or strength for patients unable or unwilling to take a dosage form that is commercially available.

September 30, 2014

Submitted electronically via www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Aaron Lopez
Senior Director of Public Affairs
PCCA

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations

Ingredient Name	Methylcobalamin
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	*Co* α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co* β-methylcobamide
Common Name(s)	Methylcobalamin, Mecobalamin
UNII Code	BR1SN1JS2W
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	JP monograph; OTC in US as a dietary supplement; Available in many countries
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Capsules, Cream, Solution
Compounded Strengths	Capsules: 1- 10 mg; Cream: 0.1 – 2.5%; Solution: 0.1 – 2.5%
Anticipated Routes of Administration	Oral, Topical, Injectable, Nasal Spray
Saftey & Efficacy Data	James SJ, et al. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009 Jan;89(1):425-30. [http://www.ncbi.nlm.nih.gov/pubmed/19056591] Frye RE, et al. Effectiveness of methylcobalamin and folinic Acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. Autism Res Treat. 2013;2013:609705. [http://www.ncbi.nlm.nih.gov/pubmed/24224089] Talaei A, et al. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. Int J Food Sci Nutr. 2009;60 Suppl 5:71-6. [http://www.ncbi.nlm.nih.gov/pubmed/19212856] Yaqub BA, et al. Effects of methylcobalamin on diabetic neuropathy. Clin Neurol Neurosurg. 1992;94(2):105-11. [http://www.ncbi.nlm.nih.gov/pubmed/1324807] Zhang M, et al. Methylcobalamin: A Potential Vitamin of Pain Killer. Neural Plast. 2013;2013:424651. [http://www.ncbi.nlm.nih.gov/pubmed/24455309]
Used Previously to compound drug products	Autism Spectrum Disorders, Neurological Disorders, Pain
Proposed use	Autism Spectrum Disorders, Neurological Disorders, Pain

Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Unless other studies performed / found: Capsule: USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier. Topical: USP <795> recommendation of BUD for water containing topical formulations – “no later than 30 days." Injection: USP <797> recommendations for high risk level compounded sterile products.

PCCA USA
9901 South Wilcrest Drive
Houston, TX 77099
Tel:281.933.6948
Fax: 281.933.6627

PCCA Canada
744 Third Street
London, ON N5V 5J2
Tel: 800.668.9453
Fax: 519.455.0690

PCCA Australia
Unit 1, 73 Beauchamp Road
Matraville, NSW 2036
Tel: 02.9316.1500
Fax: 02.9316.7422

CERTIFICATE OF ANALYSIS

PRODUCT: METHYLCOBALAMIN
ITEM NUMBER: 30-2963
LOT NUMBER: C157376
MFG. DATE: 02/28/2013
EXPIRATION: 02/27/2016

CAS: 13422-55-4
MW: 1344.3800000000
FORMULA: C63H91CoN13O14P

TEST	SPECIFICATIONS	RESULTS
Acetone	<=5000 ppm	15 ppm
Assay (dried basis)	>=98.0 %	98.8 %
Description	pass *BRIGHT RED MICROCRYSTALLINE POWDER; PRACTICALLY ODORLESS; HYGROSCOPIC; PROTECT FROM LIGHT.*	pass
Ethanol	<=5000 ppm	50 ppm
Identification	pass	pass
Loss on Drying	<=12.0 %	5.9 %
Max Related Substances	<=0.5 %	0.24 %
Solubility	pass *Soluble in water at 12.5 mg/ml; soluble in propylene glycol (50 mg/ml); soluble in alcohol producing a red clear solution.*	pass
Total Content	<=2.0 %	0.7 %

QC APPROVED
PRINT DATE: 3/3/2014

Tab 2b

Methylcobalamin
Nomination Clarification

Alliance for Natural Health USA
3525 Piedmont Road NE
Building 6, Suite 310
Atlanta, GA 30305

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
anhinternational.org

January 26, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Avenue
Building 51, Room 3249
Silver Spring, MD 20903

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman:

The Alliance for Natural Health USA (ANH-USA) is responding to FDA's questions regarding the nomination of **Methyl B12** for inclusion on the 503A bulk drug substances list.

ANH-USA is an independent, nonprofit watchdog organization of more than 550,000 members nationally that protects consumer access to natural health services, practitioners, and resources. Safely compounded medications, as provided by integrative physicians, fulfill an important clinical need for many of our members. These are patients who have not found relief for their health conditions through conventional means. Such patients often have an adverse reaction to mass-manufactured drugs, and require a more individualized treatment regimen.

Before providing our responses, we wish to object to what has apparently evolved into a new request for a disease indication rather than simply a use for the ingredient. The implication is that FDA approval will be based upon a disease indication when functional and nutraceutical uses have substantial clinical value and are plainly lawful under the Food, Drug, and Cosmetic Act.

Responses:

Q1. Does Alliance for Natural Health USA still want to pursue review by the FDA and consideration by the PCAC of methylcobalamin for inclusion on the 503A bulks list?

A. Yes

Q2. Please confirm in writing the proposed uses identified in your nomination For those uses of the nominated substance that you want FDA to review, provide scientific articles supporting each use,

and identify the dosage form and strength/concentration for each use. If you do not provide any scientific articles supporting each use for the nominated substance, FDA does not intend to review that use. Please note that the use "neuropathic disorder" is insufficiently precise to guide FDA's review.

A. ANH-USA cites the response of McGuff Compounding Pharmacy Services and the American Association of Naturopathic Physicians, both of which possess the necessary expertise on this matter.

ANH-USA appreciates the FDA's and its Pharmacy Compounding Advisory Committee's (PCAC) consideration of this further information in support of the nomination of methylcobalamin for inclusion on the 503A bulk drug substances list. We would like to reiterate that the Agency's original request asked only for ingredients' proposed use, not the disease condition or indication.

If you have further questions, please contact me.

Sincerely,

Michael Jawer
Deputy Director

Email: mike@anh-usa.org
Phone: 240-396-2171

VIA EMAIL
toni.hallman@fda.hhs.gov

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
Food and Drug Administration
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

Re: Response to Requests for More Information on Nominations for Alpha Lipoic Acid, Methyl B12 and Choline Chloride
Docket FDA-2015-N-3534

Dear LT. Hallman:

I write on behalf of the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the three above-named ingredients. It is correct that IMC and AANP maintain these nominations as ingredients that should be placed on the 503A positive list. In addition to providing what material we can in the short time provided, I write to object to the unreasonably short time allowed and request and extension to file a more complete response. Of more import, we also object to what has evolved into a new request for a disease indication rather than simply a use for an ingredient, and its implication that approval must be based upon a disease indication when functional uses have great clinical utility and are plainly lawful under the language of the Food, Drug and Cosmetic Act ("FDCA").

Enclosed please find three submissions addressing the questions raised for response by today, though we intend to supplement these filings. We also are in support of submissions made by co-nominators the Pharmacy Compounding Centers of America and McGuff Compounding Pharmacy.

Objection As to Insufficient Notice

IMC and AANP appreciate that FDA is seeking additional information as it weighs our nominations, but the due date of January 26, 2018 for much of the information was only submitted to our organizations on January 16th. A ten-day window, particularly for physicians and pharmacists engaged in full-time practices, is not reasonable. We appreciate that staff would

like time to review clinical materials prior to the as yet unannounced PCAC meeting, but the requests are quite extensive. We are therefore providing what we can in the limited time allowed but request until February 23, 2018 to supplement our responses along with the other questions requested by that date.

The request regarding alpha lipoic acid, for example, asks for at least one study for the 23 proposed indications that were submitted for that ingredient. Submissions by AANP, IMC and co-nominators McGuff Compounding Pharmacy and the Professional Compounding Centers of American have previously provided citations to over 280 articles, the indication for most which can plainly be seen in the titles as referring to diabetic neuropathy or other conditions. The statement that indications will not be reviewed unless we submit additional materials, and in a ten-day window, given the extent of the materials already provided, is concerning. Given, as well, the FDA's evident policy on ingredients under review that a single study is insufficient to gain approval, the actual burden for all three ingredients made in these requests is much higher.

Further, the request to break down the dosage and form by each proposed use is not contained in the Federal Register Notice (2015-27271) but constitutes a new request, as is the request to provide supportive statements from the materials of professional medical societies and to prioritize all uses. Further, while we appreciate that the FDA is following up on our previous submissions, the original request only asks for the "proposed use" and does not ask for the disease indication or condition. These are all significant requests that cannot be reasonably accomplished in ten days.

Objection as to Requirements of a Disease Indication

IMC and AANP object to the requirement that an ingredient demonstrate that it has an indication for a disease or condition to sustain a nomination. Such a requirement is neither clinically required nor lawful as certain ingredients are used solely for their functional effects or nutraceutical value and may not be intended to treat, cure or even prevent specific disease states. While our nominations state and we believe evidence and experience show that these ingredients indeed have a role to play in preventing, mitigating or treating disease, the presumption that an item may be refused placement on the positive list even if there may be proper and legitimate functional or nutritional uses as their sole basis is not clinically or legally grounded.

While we understand that FDA is focused on the disease model and this language might at first reading have unintentionally excluded functional uses of ingredients, FDA's briefing documents have thus far excluded consideration of functional uses. Further, the request for information for choline chloride specifically asks, for example, for the "disease state(s) or health condition(s)" we are proposing, and states that "neuropathic disorder" is insufficiently precise, suggesting not only that a disease state is required but that it must even be presented with ICD-10 or similar

specificity. A claim of treating "neuropathic disorders" would certainly qualify as an improper drug claim on an unapproved product, and basing approval upon whether a physician chooses to use choline chloride for peripheral, autonomic, diabetic or other form of neuropathy within the scope of their training seeks to apply an improperly high threshold to matters that fall within the purview of state overseen medical and compounding practice. While we appreciate the effort to focus the review of the clinical evidence, to the extent that a disease indication were the basis for use, as long as choline chloride, in this example, is shown to have a valid role in any form of neuropathy that should be sufficient to allow a physician to the ability access for their patients as guided by his or her knowledge and experience. While I won't burden this letter with the extensive citations available on the topic, the FDA's regulatory authority and jurisdiction is limited by the right of physicians to practice medicine. Compounding pharmacies are not permitted to market their ingredients with therapeutic claims in any event. Finally, the request for specificity seems plainly contrary to the lack of FDA authority to limit the use of a compounded ingredient placed on the positive list to certain indications.

The Legal Requirement for Ingredient "Use"

Imposing a disease model on compounding practice is expressly contrary to the FDCA, which defines a drug as including products that affect the function of the body. 21 U.S.C. § 321(g)(C). Nothing in that definition limits either the definition or proper use of a drug to the disease claim listed separately at 21 U.S.C. § 321(g)(B).[1] If one markets an ingredient with the sole claim that it affects physiologic function without first obtaining NDA approval, the FDA can and routinely does issue warning letters or take enforcement actions to remove such products from the market. The converse is also true; where a product provides functional support it is properly a drug that should be considered on the merits of that claim without imposing a requirement that there be a disease indication. Whether an oversight or intentional effort to remove an entire basis for use, the FDA cannot have it both ways in its interpretation of its enabling legislation.

Where a pharmacist compounds on lawful scripts for the prescriber's purpose of affecting physiologic function, such as to provide a high level of antioxidant or anti-inflammatory activity, and no claim made about disease treatment, the FDA's criteria imposes a burden of proof for a claim that was not undertaken by the pharmacist or physician and improperly restricts an entire basis for clinically proper and lawful use. Further, assessing claims has always been based upon manufacturer's intent, which is not applicable to physician prescribing.

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[1] "The term "drug" means . . (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals..." 21 U..C. § 321(g).

Nothing in the language of the Drug Quality and Security Act ("DQSA") (P.L. 113-54) or the Food and Drug Administration Modernization and Accountability Act of 1997 (P.L. 105-115) ("FDAMA") limits this definition of a "drug" nor provides any basis for restricting compounded drugs to disease indications.

Functional Uses

Support for optimal function or therapeutic support are legitimate purposes undertaken by medical and naturopathic care that are completely missing from FDA consideration. Clinical modeling and evidence of the role of antioxidants, for example, in optimal functioning are less susceptible to controlled study but the evidence for many of these ingredients for such use is nonetheless ample. Alpha lipoic acid is a potent anti-oxidant, which is a valuable support for healthy functioning. The health effects of antioxidants are well-recognized, and as an ingredient in a compounded formulation could have obvious value. Ingredients that have recognized anti-inflammatory effects[2] have been recommended for denial by FDA because of its position that physicians should not be able to offer such support to their patients unless the evidence reaches the additional threshold of evidence that it can treat a disease. The FDA did not make that part of its request of nominators in its original request, nor has not subjected the wisdom of this health policy to notice and comment, as it is but one of many major health policy decisions that are completely absent[3] from its December 16, 2015 Anticipated Notice of Proposed Rulemaking "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," failing both in its legal duties and obligations to understand the arena it is regulating.

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[2] The FDA recommended the denial of resveratrol, for example, which it considered for both for the treatment of pain and impaired glucose tolerance. In its briefing paper the FDA noted that "Resveratrol appears to have anti-inflammatory, antioxidant, anticancer, and other effects in many in vitro, ex vivo and in vivo models." November 20, 2017 PCAC meeting, Briefing Paper on Resveratrol at 29. While the FDA was concerned about bioavailability and bimodal dosing responses, this was within the context of managing disease and not an assessment of the role it can play as an antioxidant in prevention and functional support for wellness. Other examples of the complete disregard for functional purposes thus far include N-acetyl-D-glucosamine, 5-HTP (oxitriptan), alanyl-L-glutamine, acetyl-L-carnitine, and N-acetyl-D-glucosamine (recommended for disapproval for oral use).

[3] *See* nominators comments on "Proposed Rule: List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," Docket No. FDA-2016-N-3464 dated March 16, 2018.

This omission of functional care considerations has been pervasive in the ingredient review process as many of the ingredients reviewed have been ingredients marketed as dietary supplements for functional purposes. Physician prescribed combinations of nutrients may be used by physicians practicing functional medicine pursuant to schools of medical or naturopathic thought, taught in properly recognized universities or credentialed educational programs that receive ACCME Category I CME certification. This field of practice has been unrecognized and entirely overlooked in FDA's regulatory scheme; it has taken no evidence, consulted no experts in the field of nutritional, functional or naturopathic medicine, and made no findings. Our submissions of these three products provide examples of such uses and FDA should not impose a disease claim requirement where actual practice is not based on such claims. The rejection without comment of a field of recognized care is arbitrary and capricious as a legal matter and poor practice as a matter or public health policy.

Nutritional Uses

Some compounded products may also provide convenient, tailored nutrient support specific to the health needs of a patient. This promotes convenient use, avoids allergens and contaminants, and in some cases may include prescription items as part of an overall treatment and support approach. Patients may require compounded ingredients due to difficulties consuming whole foods or specific kinds of foods or benefit from dietary supplementation which provides nutrients otherwise not readily available due to special or limited diets. Creating mixtures of formulated nutraceuticals can increase patient compliance, maximize synergistic effects and assist in treating difficulties with absorption or other digestive issues. Sublingual routes of administration may also be of help with ingredients which present absorption issues in certain patients.

This is a form of compounding practice about which the FDA has taken no cognizance and thus has not addressed its value.

The Role of the United States Pharmacopeia Dietary Ingredient Monographs

The rejection of the United States Pharmacopeia ("USP") dietary ingredient monographs generally, and of specific nutraceuticals as the process moves forward, threatens to eliminate these entire methods of practice. Whether or not this is by design, the FDA has shown no signs that it is aware of this practice or the impact it's regulatory course is having upon it. There has been no discussion in the Compliance Policy Guidance documents, federal register, PCAC briefing documents or in the PCAC meetings about this practice. No voting member of the PCAC Committee has any training or experience in this form of practice. Compounding pharmacists have always been free to compound items listed in the USP and for the purposes described in this letter are an important practice that should continue.

However these issues are ultimately addressed, the FDA's requirement for a disease indication and restrictive reviews of ingredients based on a concern that physicians may use a dietary supplement for functional or therapeutic purposes ignores areas of medical and naturopathic practice outside of FDA's expertise. Physicians with training and experience in such use, whether because of anticipated therapeutic effects or unique assimilation issues should be legally allowable without each nutrient having to go through disease indication levels of scrutiny.

We would appreciate it if you would share this letter with the members of the PCAC so that our concerns may be considered directly by the Committee.

Sincerely,

Alan Dumoff

Enclosures
AANP / IMC submission for alpha-lipoic acid
AANP / IMC submission for choline chloride
AANP / IMC submission for methylcobalamin

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Alpha Lipoic Acid
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organization still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulk list?

A. Yes.

Q. Please explain whether the nominated molecule is enantiomerically pure or a racemic mixture.

A. Racemic mixture.

Q. Alpha lipoic acid is minimally soluble in water and unstable unless protected from air and light. Please provide any information available about how these issues are addressed for compounded products, especially intravenous formulations.

A. Co-nominator McGuff Compounding Pharmacy has performed a stability study on for its alpha lipoic acid compounded preparations to demonstrate formulation stability through the assigned Beyond-Use Date.

The following parameters were examined and/or tested as part of the stability program:

i. Appearance, seal
ii. Appearance, vial
iii. Appearance, preparation
iv. Foreign matter, visible particulate
v. pH
vi. Potency assay, HDLC
vii. Sterility
viii. Antitoxin
ix. Method suitability, sterility test
x. Container closure integrity
xi. Preservative effectiveness (for multi-dose vial)
xii. Preservative concentration (for multi-dose vial)

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific

article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration and compounded dosage form is a oral capsules ranging from 100 to 500 mg, topical use and parenteral injection of 25 mg/mL or 40 mg/mL concentration. The listing below includes some of the known uses for alpha lipoic acid:

Diabetic neuropathic pain [For e.g., ICD-10 E13.40; Ideopathyic Neuropathy ICD-10G60.9]. ALA is an approved treatment for diabetic neuropathy in Germany.

a. "Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy." Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Möller W, Tritschler HJ, Mehnert H. Free Radic Res 1999 Sep; 31(3): 171-9.

b. "Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy." Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R. Diabetes Care. 1999 Aug;22(8):1296-301.

c. "Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?" A Review by Mijnhout, A. Alkhalaf, N. Kleefstra, HJG. Neth J Med 2010 Apr; 68(4):158-62.

d. "Preventing complications and treating symptoms of diabetic peripheral neuropathy." Comparative Effectiveness Review Number 187. Johns Hopkins University Evidence-based Practice Center.

e. "Predictors of improvement and progression of diabetic polyneuropathy following treatment with a-lipoic acid for 4 years in the NATHAN 1 trial." Ziegler D, Low PA, Freeman R, Tritschler H, Vinik AI. J Diabetes Complications. 2016 Mar;30(2):350-6.

Pancreatic cancer [For e.g., ICD-10 D01.7]

a. "The long-term survival of a patient with stage iv renal cell carcinoma following an integrative treatment approach including the intravenous alpha-lipoic acid/low-dose naltrexone protocol." Berkson, BM and Calvo, RF. Integr Cancer Ther 2017 Dec 1 epub.

b. "Revisiting the ALA/N (a-lipoic acid/low-dose naltrexone) protocol for people

with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases." Berkson BM, Rubin DM, Berkson AJ. Integr Cancer Ther 2009 8: 416.

Hepatitis C [For e.g., ICD-10 B17.10]

a. "A conservative triple antioxidant approach to the treatment of hepatitis c combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories." Berkson BM. MEd Klin (Munich) 1999: Oct 15;94 Suppl 3:84-9.

Liver Disease, Cirrhosis and Toxic Disease [For e.g., ICD-10 K71.8]

a. "Alpha lipoic acid and liver disease." Berkson, BM. Townsend Letter, Dec 2007.

b. "Lipoic acid in liver metabolism and disease" Bustamente, J. Lodge, JK, Marcocci L, Tritschler HJ, Packer L, Rihn BH. Free Radic Biol Med. 1998 Apr; 24(6):1023-39.

Mushroom Poisoning [For e.g., ICD-10 T62.0X1A]

a. "Thioctic acid in the treatment of poisoning with alpha-amanita." Barter and Berkson.

Fibromyalgia and Muscle Pain [For e.g., M78.7]

a. "Innovations in the management of musculoskeletal pain with alpha-lipoic acid (impala trial): study protocol for a double-blind, randomized, placebo-controlled crossover trial of alpha-lipoic acid for the treatment of fibromyalgia pain." Gilron L, Tu D, Holden R, Towheed T, Ziegler D, Wang L, Milev R, Gray C. AMIR Res Protoc 2017 Mar 28;6(3).

Q. Prioritize the uses of alpha lipoic acid in order of strongest to weakest scientific support.

A. The following conditions are prioritized for the uses of alpha lipoic acid from strongest to weakest scientific support: diabetic neuropathy, hepatitis, fibromyalgia and pancreatic cancer.

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Methylcobalamin
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Methylcobalamin inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of Methylcobalamin for inclusion on the 503A bulk list?

A. Yes.

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide scientific articles supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration include oral, ranging from 500 to 5000 mcg; sublingual, ranging from 500 mcg to 5000 mcg troche or liquid; nasal, ranging from 250-500 mcg/spray 0.1 ml; and parenteral subcutaneous injection or infusions ranging from 0.5 mg/mL to 12.5 mg/mL for all listed uses for methylcobalamin below:

Autistic Spectrum Disorder [For e.g., ICD-10 F84.0]

a. "Treatments for biomedical abnormalities associated with autism spectrum disorder." Frye RE, Front Pediatr 2014 June 27;2:66.

b. "Randomized, placebo-controlled trial of methyl b12 for children with autism." Hendren RL." James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. J Child Adolesc Psychopharmacol. 2016 Nov, 26(9):774-783.

c. "Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism." James SJ, Melnyk S, Fuchs G, et al. Am J Clin Nutr. 2009;89(1):425-30.

d. "Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism." James SJ, Cutler P, Melnyk S, et al. Am J Clin Nutr. 2004 Dec;80(6):1611-7.

e. "Effectiveness of methylcobalamin and folinic acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status." Frye, RE, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters, L, James SJ. Autism Res Treat. 2013 Oct 12:epub.

Diabetic and Idiopathic Neuropathy [For e.g., ICD-10 E13.40; Idiopathic Neuropathy G60.9; Neualgia and neuritis M79.2]

a "Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials." Sun Y. Acta Neurol Taiwan. 2005; June 14(2): 48-54.

b. "Intravenous methylcobalamin treatment for uremic diabetic neuropathy in chronic hemodialysis patients." S. Kuwabara. Intern Med. 1999. Jun; 38(6):472-5.

Pain Management [For e.g. ICD-10 G89.4]

a. "Intravenous and intrathecal methylcobalamin: a potential vitamin of pain killer." Zhang. Neuro Plast 2013 Epub 2013 Dec 26.

Amyotrophic Lateral Sclerosis [For e.g., ICD-10 G12.21]

a. "Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study." Kaji R, Kodama M, Imamura A, et al. Muscle Nerve. 1998;21(12):1775-8.

b. "Neuroprotective effect of ultra-high dose methylcobalamin in wobbler mouse model of amyotrophic lateral sclerosis." Ikeda K, Iwasaki Y, Kaji R. J Neuro Sci. 2015 Jul 15;354(1-2:70-4.

Genetic Metabolic Disorders, such as MTHFR [For e.g., ICD-10 Z15.89]

a. "Anxiety and Methylenetetrahydrofolate Reductase Mutation Treated With S-Adenosyl Methionine and Methylated B Vitamins." Anderson S, Panka J, Rakobitsch R, Tyre K, Pulliam K. Integrative Medicine: A Clinician's Journal. 2016;15(2):48-52.

Q. Provide additional information you believe would be useful for us to consider.

A. There is an FDA registered medical food, METANX, with Methyl B-12 as a primary ingredient. The claim is for usefulness in multiple disorders and lists numerous references. *See* http://www.metanx.com/pdf/METANXCapsulesPIStatement.pdf
It has safety data and has been in use over 5 years. It has common allergens [MILK AND SOY] which provides an additional reason that it should be available to compound PO.

STATED INDICATIONS: METANX® is indicated for the distinct nutritional requirements of individuals with endothelial dysfunction who present with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy. METANX® is also indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia who present with lower extremity ulceration(s).

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Choline Chloride
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of choline for inclusion on the 503A bulk list?

A. Yes.

Q. Please submit in writing the disease state(s) or health condition(s) that you are proposing for the FDA's review, the dosage form and strength/concentration proposed for each use, and scientific articles in support of each use.

A, Without waiving the objections contained in the accompanying letter, at the compounded dosage and delivery of a parenteral injection of 50 mg/mL concentration as a chloride salt, the listing below includes some of the known uses for choline:

Liver Diseases; Hepatic Steatosis [For e.g., ICD-10 K70.0, K76.0]

a. "Studies on the Effects of Intravenously Administered Choline Chloride in Patients with and without Liver Disease." Stegmann. J. 1953.

b. "Choline supplementation protects against liver damage by normalizing cholesterol metabolism in Pemt/Ldlr knockout mice fed a high-fat diet." Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. J Nutr. 2014 Mar;144(3):252-7.

c. "The Addition of Choline to Parenteral Nutrition." Buchman A. Gastroenterology 2009 Nov;137 (5 Suppl):S119-128 (Steatosis).

d. "Revisiting the ALA/N (a-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases." Berkson BM, Rubin DM and Berkson AJ. Integr Cancer Ther 2009 8: 416.

Fetal Alcohol Spectrum Disorder

a. "Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders." Nguyen TT Risbud RD, Mattson SN, Chambers CD, Thomas JD. Am J Clin Nutr. 2016 Dec;104(6):1683-1692. Epub 2016 Nov 2.

Atherosclerosis

a. Lipotropic factors and atherosclerosis; action of methionine, choline and inositol on experimental cholesterol atherosclerosis. Capretti G, Paglia G. G Clin Med. 1950 Sep;31(9):1120-37.

b. ["Action of lipotropic factors in atherosclerosis"]. Concours Med. 1954 Nov 13;76(46):4207-9. [Article in French] Millot J (French)

Functional Support [For e.g., ICD-10 G31.84]

a. "Citicoline improves memory performance in elderly subjects." Alvarez XA, Laredo M, Corzo D, Fernández-Novoa L, Mouzo R, Perea JE, Daniele D, Cacabelos R Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):201-10.

February 23, 2018

VIA EMAIL
toni.hallman@fda.hhs.gov

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
Food and Drug Administration
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

Re: Response to Requests for More Information on Nominations for Methylcobalamin and Alpha-Lipoic Acid
Docket FDA-2015-N-3534-0001

Dear LT. Hallman:

I write on behalf of and the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the above-named ingredients.

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In the enclosed materials we provide additional information about historical and current uses.

Sincerely,

Alan Dumoff

Enclosures
Additional AANP / IMC submission for methylcobalamin and alpha-lipoic acid
Full journal articles as noted in the attached bibliographies

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Methylcobalamin
Submitted February 23, 2018

Additional References

Tamura J, Kubota K, Murakami H et al. Immunomodulation by vitamin B12: augmentation of CD8þT lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immu- nol (1999) 116,28 - 32.

Shibuya K1, Misawa S, Nasu S et al. Safety and efficacy of intravenous ultra-high dose methylcobalamin treatment for peripheral neuropathy: a phase I/II open label clinical trial. Intern Med. 2014;53(17):1927-31. Epub 2014 Sep 1.

Prousky, JE. Understanding the Serum Vitamin B12 Level and its Implications for Treating Neuropsychiatric Conditions: An Orthomolecular Perspective. JOM 25:2 (2010).* (PDF attached).

Xu Q, Pan J, Yu J et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. Diabetes Res Clin Pract. 2013 Aug;101(2):99-105. doi: 10.1016/j.diabres. 2013.03.033. Epub 2013 May 9.*

Historical Use Data

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In addition we provide the following:

Physician comments submitted to AANP about the current clinical and historical reasons for using methylcobalamin:

Note in the following physician statements the need for compounded, injectable dosages including the absorption difficulties or tolerance for oral dosing faced by many patients; the need for this form of B12 including genetic defects and specific processing problems for cyanocobalamin; specific case reports of various ailments and for proper immune function; and financial reasons why compounded versions should be available. These represent a small sample of the clinical and historical bases for use:

“I have used many of these compounded substances in my practice for a variety of patient specific needs. In fact I have never used as B12 other than methylcobalamin for IM or IV applications as the majority of the American population has an MTHFR SNP I would give the

activated form to all patients without adverse events.

I have used L-glutathione (L-GSH) IV to support detoxification as this is our bodies most powerful antioxidant, specifically in people who are detoxifying from drug/etoh use and heavy metal/chemical/mold exposures. 1000-2000 mg qwk GSH IV in Parkinson's disease has improved symptoms regardless if they are using carbidopa-levodopa or other pharmaceuticals to improve symptoms. In addition to IV GSH I typically add in oral GSH. PMID: 8938817, 19230029. I have used IV ALA, choline, and quercetin less frequently, though, with symptomatic improvements and no adverse events.

These compounded substances have been beneficial to numerous patients in my practice. It is important to maintain access for patients to these high quality compounded substances. I'm grateful to McGuff Compounding for providing outstanding service and products for our patients and continuing to stand for compounded substances.

Audrey Schenewerk, ND, MS"

"I have been a practicing ND now for 18 years. I have yet to see a medicine that provides the expedient relief that intramuscular injections of methylcobalamin does for fibromyalgia patients. Many of these patients have suffered many years with the debilitating fatigue, insomnia and pain issues characteristic of this disorder. In many cases, these patients have positive tests for the inability to process synthetic forms of B12 (cyanocobalamin). Methylcobalamin bypasses this problematic biochemistry and provides the activated nutrient essential to recovery for these patients. In addition, the injectable form bypasses the GI system, which is also often problematic with this disorder. We just do not get the results with oral dosing of methylcobalamin that we see with the injectable.

I urge the FDA to consider the many thousands of patients of this sort who would be denied access to a safe and effective medicine. Please retain methylcobalamin availablility through our local compounding pharmacies.

Joanne M. Hillary PhD, ND
Hillary's Health
9103 N. Division St.
Spokane, WA 99218"

"I am writing a patient account in support of the compounding of methylcobalamin.

I have a patient who has pernicious anemia and genetic mutations affecting her methylation. She has seen improvements since doing injectable cyanocobalamin. However, we changed her injections to methylcobalamin 2 months ago and her energy has been steadily and dramatically improving in a way we have not seen with any other form of injectable cobalamin. She has been

able to exercise and is also sleeping better since this change. This has had a profound impact on her daily life, her work, her relationships, and what she feels is possible for her future. Without the methylcobalamin, I have every reason to believe she will lose these improvements since that was the only thing in her treatment that changed to correlate with these improvements.

Kimberly Hindman, N.D., L.Ac."

"Clinical case: Parkinson's disease.
60yr female, Height: 5"0" weight 110lbs.
Patient presented with neuropathy and common PD tremors in hands and legs as well as with muscles pain and stiffness, worse in her legs. Clinical investigation with cyanocobalamin IM injections to relieve symptoms revealed that 1,000mcg/mL, 1mL total volume, gave significant improvement in symptoms within a few hours of injection. Additionally, the patient found that she had more energy to complete activities of daily living, including cooking and cleaning, than she had had in years. She was functioning near normally to her and her family's astonishment. She felt her PD symptoms were about 80% better.

In an attempt to optimize her B12 status and symptom relief, 2,000 mcg were injected. While the patient did get benefit from her neuropathy, muscle stiffness and tremors, she experienced a slight sensation of being "amped up" which meant she felt her heart rate was slightly elevated and had a feeling of being jittery. This subsided within a few hours.

Ultimately, the patient's symptoms were found to be best treated with a 12,000 - 15,000mcg dose. This is only available through compounding.

This patient deserves for her symptoms to be better than 80%, which is what a single commercially available dose provides. If compounding of cyanocobalamin is unavailable to her, she will be forced to pay double for her injectable medication (already not covered by her insurance) and discard 50% of a vial. Why should she have to waste her B12 injectable material and pay more?

Dr. Nicole Anderson"

"I have been using methylcobalamin in my practice for over a year. This compounded vitamin has changed literally hundreds of my patients lives. I have seen the following:
- reduced anxiety
- improved stress response
- weight loss
- improved sleep
- general mood improvement
- reduced aggression
- improved immune health

All of these benefits have been reported by my patients. Many of these patients had sought out pharmaceuticals to address all of the above conditions without any reprieve. Many patients had sought out cyanocobalamin or hydroxycobalamin injections previously without any benefit. We are seeing an increase in patients with methylation difficulties, and removing methylcobalamin would be incredibly detrimental to their health.

Dosing:
IM: 2.5 mg biweekly
IV: 5 mg monthly

Dr. Elisse Evans, ND
Origins Integrative Medicine
originsintegrative.com
928 Garden St. Ste. 1
Santa Barbara, CA
805-203-6877”

“This is an essential ingredient in neuro-regenerative protocols and fatigue care for many patients (fibromyalgia, epstein barr virus, etc).

As a concerned and very hard working physician I would like to tell you about a few patients I have who need the Methylcobalamin (B12) in particular. First they have genetic defects that affect their body processing B12 orally, second they have nausea and even vomiting if they take Methylcobalamin or any other B-Vitamins orally. These folks need the injectable types of B12 and B-vitamins or they will remain ill. I have a number of clients who also receive Glutathione for various health concerns and getting this again as an oral supplement is unworkable as it is very un-absorbable through the GI system.
- Methycobalamin
- Quercitin
- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

Dr. DeeAnn G. Saber, NMD is part of Wellness First!, a collaborative, holistic community of practitioners in Tucson, AZ, dedicated to personal integrity, professionalism, and service.
Transformational Medicine, PLLC
3861 North First Avenue
Tucson, AZ 85719
Office# 520-209-1755
Cell# 520-668-0039
DrDeeAnnND@aol.com
www.3861WellnessFirst.com”

“Methylcobalamin is the form of vitamin B12 that can be used immediately without modification or conversion in the body. This is especially important for people with genetic mutations that make it difficult to activate compounds in the body by methylation. Methylcobalamin is especially important for immune health. Deficiency of Methylcobalamin in humans has been shown in research to decrease lymphocytes and suppress natural killer (NK) cell activity. NK cells are a type of white blood cell that attack cells infected by viruses. Supplementation of Methylcobalamin provides patients with the defenders necessary to stay healthy. Methylcobalamin has been especially helpful in reducing homocysteine levels in many patients. It is imperative for us to allow IV and IM compounded Methylcobalamin for patients who are unable to take it orally, and for patients who have digestive issues such as Celiac disease and IBD that prevent them from absorbing oral vitamins.

Dr. Samantha Larkin, ND”

“My first patient, 20 years ago, was a 40-something artist with severe neurological impairments. She had over $50,000 in tests performed, a lot of money for tests in those days. Finally her neurologist told her to put her affairs in order as she did not have much time left to live. She gave away and sold everything for her last hurrah, a trip to Mexico. On the recommendation of a friend of hers she came to me just before taking her trip. I gave her a homeopathic remedy and started her on 5 mg IM methylcobalamin daily. Within a week she was fine. She came back from her Mexico trip and was not sure what to do as she had to find a job, a place to live, and restock with all the things she needed to live.

About 10 years ago, a woman brought her ten-year old autistic son to me. She had already begun numerous treatments which were showing promise. One of them was 5 mg methylcobalamin every other day, slowly tapering down. Another was hyperbaric oxygen therapy. With continued treatment he went on to become completely normal. As a matter of fact,
the school principal, who fancied himself an expert on learning disabilities, told the mother that her son was not autistic and could not have been. He became one of the most popular boys in his class, a magnet for girls as his mother described him.

About five years ago I had a cancer patient who was suffering severe after-effects of conventional treatments. The main thing I offered was 10 mg doses of methylcobalamin. The patient recovered very quickly from the toxic effects of the conventional treatments.”

“From: Michael Traub ND, FABNO
[Excerpt]

Dear Committee members:

I understand you are asking for additional information to defend why these following ingredients

should be reviewed and included in the 503A bulk drug substances list:

- Methylcobalamin
- Quercetin
- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

I have been using these agents safely and successfully for many years and I would like to urge you to include these substances in the 503A bulk drug substances list. They are extremely valuable and I would like to share one anecdote that exemplifies this:

On April 25, 2016 I was consulted by a 69 year old woman complaining of pain in her hands and feet of several months duration, with erythema and dry skin, as a result of chemotherapy-induced peripheral neuropathy from Taxotere that she had received for localized inflammatory breast cancer. Two days later she returned to my clinic and received an intravenous infusion of alpha lipoid acid 250 mg and followed by an intramuscular injection of methylcobalamin 5 mg. The following day she reported that her pain, the erythema and dry skin had all completely resolved within the prior 24 hours.

To this day (February 20, 2018), there has been no recurrence of any symptoms of the peripheral neuropathy, and the patient is asymptomatic with minimal residual disease.

This case is just one of many of my patients that have benefitted from the valuable agents in questions. Please use your authority to preserved their availability.

Thank you.

Sincerely,

Michael Traub ND, DHANP, FABNO
Primary Care Medicine
Board Certified in Naturopathic Oncology
Founder and Medical Director
Lokahi Health Center
75-169 Hualalai Rd, Suite 301
Kailua Kona, HI 96740
Phone 808.329.2114
Fax 808.326.2871
mtraubnd@me.com
michaeltraubnd.com”

"To Whom It May Concern:

As a naturopathic doctor, I often use methylcobalamin as a treatment because many of my patients are truly deficient in vitamin B12. The nutrient deficiency is first confirmed via lab testing and dosing is dependent on the degree of deficiency and how well the patient tolerates the medicine. Methylcobalamin is the bioactive form of vitamin B12, therefore, is easier to absorb and I find the diverse forms (i.e. oral, IV, sublingual, etc) afford better compliance for the patient. Methylcolabamin has been key in helping me to treat fatigue, inflammation, eczema, toxic overburden, and more. Given it is also water soluble, this naturally limits the risk of overdosing as well. . .

Dr. Ray, ND MS: The People's Doctor
(Revée Barbour, CA Lic#: 868)
1215 K Street, 17th Floor
Sacramento, CA 95814
Ph#: (916) 503-3189
Fax#: (916) 415-1979
Email: Ray@DrRayND.com
Website: www.DrRayND.com"

Patient Comments submitted to AANP about their experience with methylcobalamin
(Names withheld for privacy):

"I have used both methylcobalamine and cyanocobalamine and strongly prefer methyl. I have had weekly B12 shots for many years due to a medical condition and ask that it remain available."

"I have a genetic fault/mutation found through MTHFR DNA Analysis. The two mutations (C677T and A1298C) combine to greatly inhibit my absorption of B12 through my diet. The mutations were discovered by (b) (6) ND about 4 years ago when I consulted her for symptoms of pernicious anemia including peripheral neuropathy, burning tongue, burning and tingling in my thighs and feet and hands. After this discovery Dr. (b) (6) suspected that I was B12 deficient and ordered weekly injections of 2.0 cc of methylcobalamin combined with 0.5 cc of Vitamin B complex. My symptoms greatly diminished over the next 2 to 4 weeks after starting the injections. On two different occasions over the past 4 years I stopped the B12/ methycobalamin injections and my symptoms returned."

"I urge the FDA and the PCAC not to restrict the availability of methylcobalamin. It is absolutely critical to my health and well being. It turns out that my body cannot convert the other available forms of cobalamin e.g. cyanocobalamin, into the methyl form which I require."

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Alpha-Lipoic Acid
Submitted February 23, 2018

Additional Indications: Improves insulin-resistance and glucose disposal in type 2 diabetes, chronic fatigue
(Natural Medicines Database)

Additional Dosing Information: Administered intravenously in dosages no greater than 600 mg. Impaired glucose tolerance: 250mL of saline solution containing 600mg ALA. Ischemia-reperfusion injury protection: A dose of 600mg of alpha-lipoic acid in 50mL of sodium chloride. Type 2 diabetes: Alpha-lipoic acid 500-600mg in saline. (Natural Medicines Database)

Attached, *see* the application to amend schedule of substances under the General Regulation of the College of Naturopaths of Ontario and the clinical study data listed there.

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Historical Use Data

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In addition we provide the following:

Physician comments submitted to AANP about the current clinical and historical reasons for using alpa lipoic acid:

To Whom It May Concern:

Alpha lipoic acid (ALA) is one of my miracle nutrients for treating resistant cases of diabetes type 2, drug-induced polyneuropathy, and neuro-inflammation. Recently, one of my patients reduced her HgbA1c from 7.2 to 6.2 after only 3 months of taking ALA at 600mg, BID. A couple other patients have almost complete resolution of peripheral neuropathy in their fingers and toes as a side effect of their chemotherapy.

Dr. Ray, ND MS: The People's Doctor
(Revée Barbour, CA Lic#: 868)
Naturopathic Doctor & Life Coach
1215 K Street, 17th Floor
Sacramento, CA 95814
Ph#: (916) 503-3189
Fax#: (916) 415-1979
Email: Ray@DrRayND.com
Website: www.DrRayND.com

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α-Lipoic acid can improve endothelial dysfunction in subjects with impaired fasting glucose

Guangda Xiang*, Jinhui Pu, Ling Yue, Jie Hou, Huiling Sun

Department of Endocrinology, Wuhan General Hospital of Guangzhou Command, Wuhan 430070, Hubei Province, PR China

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Abstract

Several studies showed that impairment of endothelium-dependent arterial dilation (EDAD) exists in subjects with impaired fasting glucose (IFG). The crucial mechanism of this endothelial dysfunction remains unclear. We hypothesized that oxidative stress may be partially responsible for the impairment in EDAD in subjects with IFG. Thus, the present study was designed to assess whether the antioxidant α-lipoic acid can improve endothelial dysfunction in subjects with IFG. Sixty subjects with newly diagnosed IFG and 32 healthy individuals with normal glucose tolerance were enrolled. Subjects were randomized into 2 groups: untreated experimental group (n = 30) and α-lipoic acid treatment group (n = 30, α-lipoic acid 600 mg via intravenous infusion once a day for 3 weeks). We measured EDAD at baseline and after 3 weeks of intervention. At baseline, EDADs in α-lipoic acid and untreated experimental groups were 4.03% and 4.14%, respectively, which were significantly lower than that in controls (5.72%) ($P < .001$). After 3 weeks of intervention, there was a remarkable increase in EDAD (reaching 5.10%; ΔEDAD, 26.5%) ($P < .01$) and a significant decrease in plasma thiobarbituric acid reactive substances (TBARS) (29.1%) ($P < .05$) in IFG subjects treated with α-lipoic acid. Endothelium-dependent arterial dilation and TBARS remained unchanged before and after intervention in the untreated experimental group. The absolute changes in EDAD showed a significant negative correlation with the changes in TBARS ($r = -0.444$, $P = .014$). Our data showed that IFG subjects have impaired endothelial function and that antioxidant α-lipoic acid can improve endothelial function through a decrease of oxygen-derived free radicals.

In 1999, the American Diabetes Association introduced the concept of impaired fasting glucose (IFG), a prediabetic state initially defined by fasting plasma glucose of 110 to 125 mg/dL (6.1-6.9 mmol/L), in which those afflicted were significantly more likely to develop diabetes [1-3]. However, for nonfatal and fatal cardiovascular disease among participants with IFG, the evidence is less consistent [4,5].

Endothelial dysfunction represents a very early step in the development of atherosclerosis [6]. The reduced nitric oxide (NO)–mediated endothelium-dependent arterial vasodilation (EDAD) occurring in endothelial dysfunction is a predictor of cardiovascular risk in high-risk subjects [7], and its improvement seems to predict treatment-induced risk reduction. Several studies have shown that endothelial dysfunction exists in subjects with IFG [8,9] and that regular aerobic exercise training can improve endothelial dysfunction [9]. However, the crucial mechanism of endothelial dysfunction in subjects with IFG remains unclear.

Recently, it was well documented that the endothelium can generate oxidative stress in the presence of cardiovascular risk factors [10] and that oxidative stress can damage endothelial function [11]. Subjects with IFG are characterized by chronic inflammation [12], dyslipidemia [9], and endothelial dysfunction [9], as well as the increased prevalence of atherosclerotic lesions and cardiovascular events [4]. Recently, one study showed that the plasma concentration of coenzyme Q_{10}, a potent lipophilic antioxidant, is significantly decreased in subjects with IFG compared with healthy subjects [13]. Therefore, we hypothesized that oxidative stress may be partially responsible for the impairment in EDAD in subjects with IFG. Thus, the present study was designed to assess whether the antioxidant α-lipoic acid can improve endothelial dysfunction in subjects with IFG.

* Corresponding author. Fax: +86 02768878410.
E-mail address: guangda64@hotmail.com (G. Xiang).

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1. Subjects and methods

1.1. Subjects

From January 2004 to January 2008, a total of 60 subjects with IFG referred to our hospital for healthy examination (age range, 42-65 years of age; mean, 58 ± 8 years) were studied. All subjects with IFG were newly diagnosed with 75-g oral glucose tolerance test performed twice within 2 weeks, and the diagnosis of IFG fulfilled the diagnostic criteria proposed by the American Diabetes Association [1]. During the same period, 32 healthy individuals with normal glucose tolerance (age range, 40-67 years; mean, 59 ± 9 years) were selected as controls. All individuals were not related. Obese (body mass index >30 kg/m^2) subjects, smokers, and those with hypertension, clinically detectable coronary artery disease, and other diseases were excluded from the study. In addition, no subject was taking any drugs, such as estrogen supplements, thyroxine, diuretics, or antihypertensive or hypolipidemic drugs. All subjects gave informed consent. The study protocol was in agreement with the guidelines of the ethics committee at our hospital.

1.2. Study design

All eligible individuals, including 60 subjects with IFG and 32 healthy individuals with normal glucose tolerance underwent brachial arterial study described below, after which subjects were divided into either the α-lipoic acid group (α-lipon 300 Stada manufactured by STADApharm, Bad vilbd, Germany) or the untreated experimental group, with 30 cases in each group. The α-lipoic acid group (250 mL 0.9% sodium chloride + 600 mg α lipon 300) was treated via intravenous infusion at a rate of 4 mL/min once a day for 3 weeks. The untreated experimental group only received 250 mL 0.9% sodium chloride via intravenous infusion at a rate of 4 mL/min once a day for 3 weeks.

1.3. Laboratory methods

Venous blood was collected after a 12-hour fast at baseline for all subjects and at 3 weeks for IFG subjects. Serum lipids, lipoproteins and other parameters, serum total cholesterol (TC) (reference range, 3.10-5.69 mmol/L), low-density lipoprotein cholesterol (LDL-C) (reference range, 2.10-3.10 mmol/L), triglycerides (reference range, 0.41-1.88 mmol/L), and high density lipoprotein cholesterol (HDL-C) (reference range, 1.16-1.82 mmol/L) were measured enzymatically. Apolipoprotein (Apo) A-1 (reference range, 1.01-1.50 g/L) and Apo B (reference range, 0.74-1.20 g/L) were measured by immunoturbidimetry. Serum lipoprotein (a) (Lp[a]) concentration (reference range, 0-300 mg/L) was measured by an enzyme-linked immunosorbent assay method. Blood glucose levels (including fasting blood glucose [FBG] and postprandial 2-hour blood glucose [2-h BG]) were measured by a glucose oxidase procedure. C-reactive protein (CRP) concentration was measured by using the CRP (latex) ultrasensitive assay (reference range, 0-3.0 mg/L). Nitrite/nitrate, stable metabolites of NO, was measured using the method reported by Kawano et al [14]. The plasma lipid peroxide content was determined using thiobarbituric acid reactive substances (TBARS) as markers [15,16]. Briefly, 2.0 mL of trichloroacetic acid–thiobarbituric acid–HCl reagent was added to 1.0 mL of sample and vortexed. To minimize peroxidation during the assay procedure, butylated hydroxytoluene was added to the thiobarbituric acid reagent mixture. Results were expressed as malondialdehyde equivalent content (nanomoles MDA per milliliter plasma). The intraassay coefficients of variation for these assays were 1% to 2% (TC, HDL-C, blood glucose, CRP), 2% to 3% (LDL-C, nitrite/nitrate), 2% to 4% (Apo A-1, Apo B, and TBARS), and 4% to 7% (Lp[a]).

1.4. Brachial arterial study

The vascular studies of the brachial artery were performed noninvasively, as described by us previously [9,17,18]. High-resolution ultrasound was used to measure changes in arterial diameter in response to reactive hyperemia (with increased flow producing an endothelium-dependent stimulus to vasodilation) and to glyceryltrinitrate (GTN, an endothelium-independent vasodilator) (128XP/10 with a 7.0-MHz linear array transducer; Acuson, Mountain View, CA). The intra- and interobserver variability in our laboratory for repeated measurements of artery diameter was 0.09 ± 0.10 and 0.08 ± 0.13 mm, respectively.

The subjects rested in the supine position for 10 minutes before the first scan and remained supine throughout the study. The target artery (the brachial 2-15 cm above the elbow) was scanned in longitudinal section, and the center of the vessel was identified when the clearest images of anterior and posterior walls of the artery were obtained. The transmit zone was set to the level of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen to vessel wall interface. Images were magnified with the resolution box function leading to a television line width of approximately 0.05 mm. Machine settings were kept constant during each study.

Flow increase was induced by inflation of a blood pressure tourniquet placed around the forearm distal to the target artery to 300 mm Hg. The cuff was released after 5 minutes; and after cuff deflation, the artery was scanned continuously for 90 seconds. Fifteen minutes was allowed for vessel recovery; sublingual GTN (400-μg spray) was then administered; and 5 minutes later, the last scan was done. The electrocardiogram was monitored continuously.

Vessel diameter was measured by 2 observers unaware of clinical details and the stage of the experiment. The arterial diameter was measured at a fixed distance from an anatomical maker, such as a bifurcation, with ultrasonic calipers. Measurements were taken from the anterior to the posterior “m” line at end diastole, incident with the R wave on the electrocardiogram. The mean diameter was calculated

Table 1
Clinical and biochemical characteristics in IFG subjects before and after intervention as well as in control groups

	Control group	α-Lipoic acid group		Untreated experimental group	
		Before therapy	After therapy	At baseline	After intervention
No. of subjects	32	30	30	30	30
Age (y)	59 ± 9	58 ± 10	58 ± 10	58 ± 9	58 ± 9
Sex (M/F)	18/14	16/14	16/14	15/15	15/15
SBP (mm Hg)	111.8 ± 7.9	113.5 ± 9.6	116.1 ± 10.2	116.6 ± 8.0	112.3 ± 9.9
DBP (mm Hg)	72.5 ± 6.4	74.1 ± 7.1	75.3 ± 8.2	74.9 ± 7.9	72.7 ± 6.6
BMI (kg/m^2)	23.8 ± 2.1	23.3 ± 1.8	23.3 ± 1.6	23.6 ± 1.5	23.9 ± 1.8
FBG (mmol/L)	4.65 ± 0.67	6.62 ± 0.52†	6.50 ± 0.48†	6.58 ± 0.53†	6.52 ± 0.54†
2-h BG (mmol/L)	6.83 ± 0.85	6.97 ± 0.81	6.88 ± 0.90	6.86 ± 0.83	6.84 ± 0.79
TC (mmol/L)	4.27 ± 0.49	5.15 ± 0.56†	5.21 ± 0.52†	5.22 ± 0.50†	5.25 ± 0.61†
LDL-C (mmol/L)	2.06 ± 0.44	3.47 ± 0.57†	3.41 ± 0.53†	3.52 ± 0.51†	3.48 ± 0.53†
HDL-C (mmol/L)	1.22 ± 0.30	1.19 ± 0.35	1.20 ± 0.38	1.21 ± 0.41	1.18 ± 0.33
Triglyceride (mmol/L)	1.28 ± 0.68	2.04 ± 0.93†	1.95 ± 0.85†	2.12 ± 0.83†	2.09 ± 0.92†
Apo A-1 (g/L)	1.23 ± 0.27	1.20 ± 0.24	1.22 ± 0.26	1.19 ± 0.28	1.22 ± 0.27
Apo B (g/L)	1.07 ± 0.22	1.12 ± 0.30	1.12 ± 0.26	1.15 ± 0.24	1.13 ± 0.25
Lp(a) (mg/L)	172 (30, 292)	159 (41, 291)	163 (38, 290)	155 (48, 310)	162 (45, 306)
CRP (mg/L)	1.28 ± 0.32	1.99 ± 0.30*	1.58 ± 0.25*	1.86 ± 0.41*	1.79 ± 0.35*
TBARS (nmol/mL)	1.58 ± 0.52	2.47 ± 0.54*	1.75 ± 0.57‡	2.41 ± 0.59*	2.25 ± 0.66*
Nitrite/nitrate (μmol/L)	60.94 ± 8.45	61.24 ± 7.83	60.11 ± 8.23	61.73 ± 8.03	60.48 ± 8.51

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* $P < .05$.
† $P < .001$, compared with control.
‡ $P < .05$, compared with subjects before treatment.

from 4 cardiac cycles. For the hyperemia scan, vessel diameter was measured 45 to 60 seconds after cuff release. Diameter changes were derived as percentage change relative to the first baseline scan (100%). Baseline blood flow (measured during the first baseline scan) was estimated by multiplying angle-corrected, pulsed Doppler recordings of the flow-velocity integral by JI and the square of the radius of the artery.

1.5. Statistical methods

Data were reported as the mean ± SD. Data among different groups were compared with analysis of variance. The difference in each parameter between before and after treatment was compared using the Student *t* test (2-tailed) for paired data, and that between patients and controls was compared by the Student unpaired *t* test. Correlations were determined by Spearman analysis. The Lp(a) concentrations were log-transformed before analysis. All analyses were carried out by using the statistical package SPSS 11.5 (SPSS, Chicago, IL).

2. Results

The clinical characteristics and biochemical results of the control subjects and α-lipoic acid as well as untreated experimental groups are given in Table 1. At baseline, FBG, TC, triglyceride, LDL-C, CRP, and TBARS concentrations were significantly higher in subjects with IFG (including α-lipoic acid and untreated experimental groups) than those in control ($P < .001$). Other parameters, that is, systolic blood pressure, diastolic blood pressure, and 2-h BG, did not differ among control and α-lipoic acid as well as untreated experimental groups ($P > .05$). The vascular characteristics of the groups are listed in Table 2. Endothelium-dependent arterial dilations in α-lipoic acid and untreated experimental

Table 2
The results of brachial artery studies in IFG subjects before and after intervention as well as in control groups

	Control group	α-Lipoic acid group		Untreated experimental group	
		Before therapy	After therapy	At baseline	After intervention
No. of subjects	32	30	30	30	30
Baseline vessel (mm)	3.85 ± 0.73	3.83 ± 0.76	3.91 ± 0.66	3.88 ± 0.62	3.87 ± 0.72
Baseline flow (mL/min)	79.75 ± 33.44	80.12 ± 30.65	79.44 ± 35.54	80.38 ± 32.52	81.14 ± 35.26
EDAD (%)	5.72 ± 0.61	4.03 ± 0.52†	5.10 ± 0.54* ‡	4.14 ± 0.56†	4.23 ± 0.63†
GTN-induced dilation (%)	20.05 ± 2.23	20.48 ± 2.42	21.36 ± 2.51	20.333 ± 2.28	21.2 ± 2.38

* $P < .05$.
† $P < .01$, compared with control.
‡ $P < .05$, compared with subjects before treatment.

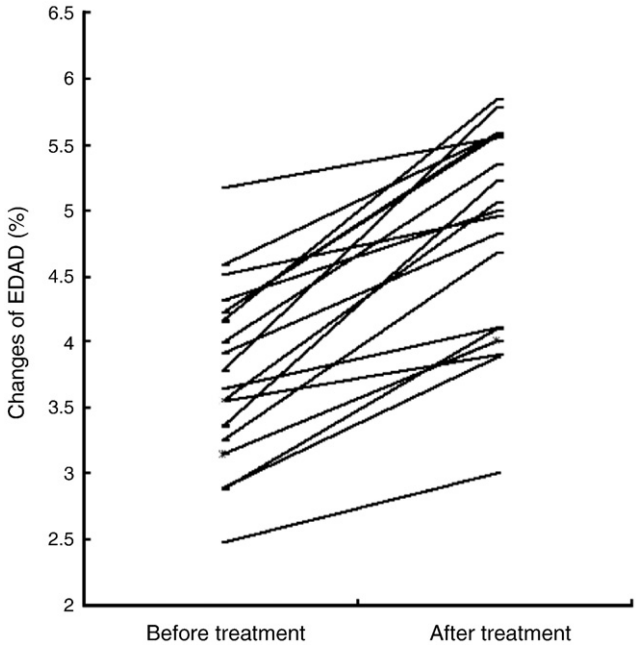

Fig. 1. Changes of EDAD before and after treatment in α-lipoic acid group.

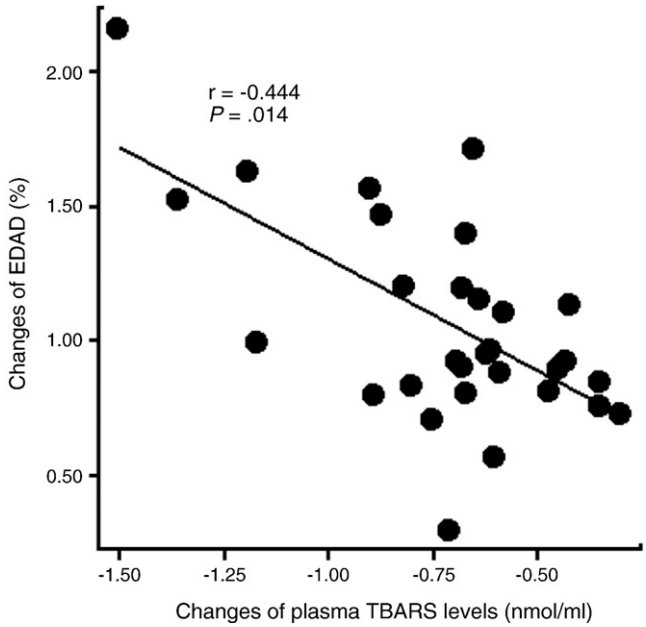

Fig. 2. Spearman correlation analyses to evaluate correlation of change in EDAD with change in TBARS before and after treatment in α-lipoic acid group.

groups were 4.03% and 4.14%, respectively, which were significantly lower than that in control (5.72%) ($P < .001$). The baseline vessel size (diameter), GTN-induced arterial dilation, and baseline flow were not significantly different among the 3 groups ($P > .05$).

After 3 weeks of intervention, there was a remarkable increase in EDAD (reaching 5.10%; ΔEDAD, 26.5%) in IFG subjects treated with α-lipoic acid ($P < .01$). As shown in Fig. 1, all subjects showed a marked increase in EDAD during the course of treatment intervention. Other vascular parameters such as baseline vessel and baseline flow did not change markedly in both α-lipoic acid and untreated experimental groups (Table 2). Furthermore, a significant decrease in TBARS (29.1%) was observed over the α-lipoic acid treatment period ($P < .05$). Other clinical parameters such as serum lipids and glucose (including FBG and 2-h BG) did not significantly change during the intervention period in both α-lipoic acid and untreated experimental groups (Table 1).

To reveal the possible causes of EDAD changes before and after α-lipoic acid therapy in IFG subjects, Spearman correlation coefficient was calculated between changes in EDAD and those in TBARS. The absolute changes in EDAD showed significant negative correlation with the changes in TBARS ($r = -0.444$, $P = .014$) (Fig. 2).

3. Discussion

The current study demonstrates that impaired EDAD exists in subjects with IFG and improves significantly after 3 weeks of α-lipoic acid treatment. However, it was still lower than that in control. The results suggest that endothelial dysfunction in subjects with IFG may be related in part to oxidative stress. As far as we know, this is the first report on the relation between endothelial dysfunction and oxidative stress in subjects with IFG.

Previous studies have suggested an association between IFG and atherosclerosis [19-21]. In a population-based cohort of middle-aged men and women, IFG emerged as an independent risk factor for atherosclerosis [20]. Recently, several studies showed that impairment of EDAD exists in subjects with IFG [8,9]. In the present study, the results are in good agreement with those reported in the previous studies [8,9]. The possible explanations for the impairment of endothelial function in IFG subjects are as follows: (1) Multiple studies have found that elevated plasma TC, LDL-C, and TG levels were related to the attenuation of EDAD [9,17,18]. Therefore, endothelial dysfunction in IFG is partially dependent on the altered lipid profiles observed in this study. (2) C-reactive protein has been recently considered as a potential contributor to inflammatory diseases including atherosclerosis as well as a marker of cardiovascular risk [22]. More recently, several studies suggested that elevated plasma CRP level is associated with endothelial dysfunction in IFG and diabetes [9,17,18]. In the present study, our results showed that plasma CRP levels in IFG subjects were significantly higher than those in controls. Therefore, inflammation may partially contribute to the impaired endothelial function in IFG subjects. (3) It has been reported previously that FBG is associated with endothelial function in subjects with IFG [9]. In the present study, we also find similar results. This may be partially responsible for the impaired endothelial function at baseline.

Endothelium-dependent arterial dilation has been shown to be mediated by the endothelium-derived relaxing factor, which is now identified as NO [23]. Previous studies have established that oxygen-derived free radicals interfere with or destroy endothelial function by inactivating NO in normal vessels [24,25]. Plasma TBARS, a marker of oxygen-derived free radicals, are associated with EDAD in subjects with impaired glucose tolerance [26]. Reversing oxidative stress and the subsequent inhibition of lipid peroxidation should improve endothelial function. Paolisso et al [27] used 600 mg vitamin E per day in a double-blind trial and showed that 8 weeks of treatment improved EDAD of the brachial artery in type 2 diabetes mellitus. Vitamin C also can prevent the endothelial dysfunction that has been observed during transient hyperglycemia after oral glucose loading in healthy subjects [28]. Coenzyme Q_{10} is a lipid-soluble molecule derived mainly from endogenous synthesis. It plays an essential role as an electron carrier in mitochondrial oxidative phosphorylation [29] and may have an important role as an antioxidant [30]. Watts et al [31] demonstrated that coenzyme Q_{10} supplementation improves endothelial function of conduit arteries of the peripheral circulation in patients with type 2 diabetes mellitus.

α-Lipoic acid functions as a cofactor in multienzyme complexes, including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched-chain α-keto acid dehydrogenase [32]. α-Lipoic acid and its reduced form, dihydrolipoate, are potent antioxidants. They are amphiphilic and widely distributed in both cell membrane and cytosol. α-Lipoic acid has been used in Germany for patients with neuropathy for more than 30 years and is considered to be safe and efficacious for treatment of diabetic symptomatic polyneuropathy [33]. In 2010, one study showed that oxidative stress contributes to endothelial dysfunction and that α-lipoic acid improves NO-mediated vasodilation in diabetic patients [34]. Recently, another study suggested that α-lipoic acid improves endothelial dysfunction induced by acute hyperglycemia during oral glucose tolerance test in impaired glucose tolerance [26]. However, the effects of α-lipoic acid on endothelial function in subjects with IFG have not been demonstrated. In the present study, plasma TBARS levels decreased markedly after 3 weeks of α-lipoic acid treatment. Moreover, the absolute changes of TBARS were negatively correlated with those of EDAD during α-lipoic acid treatment. Other clinical and biochemical characteristics including lipid profiles and CRP did not change significantly before and after treatment. It is suggested that reversing oxidative stress is partially responsible for the improvement of endothelial function by α-lipoic acid. In contrast, the serum levels of nitrite/nitrate, the metabolites and the marker for production of NO, did not differ in any of the groups before and after treatment. Because the nitrite/nitrate concentration includes the oxidative products of NO [35], endothelial dysfunction exists in IFG subjects, probably through an increase of oxygen-derived free radicals and not through a decrease in production/release of NO, and results in a quenching of NO. α-Lipoic acid improves endothelial dysfunction by a decrease of oxygen-derived free radicals.

After 3 weeks of α-lipoic acid treatment. plasma TBARS levels were close to the controls; however, EDAD was still markedly lower than that in controls. This may be due to the higher levels of TC, TG, LDL-C, and CRP.

Some limitations of the present study should be mentioned. Firstly, 2 studies from one group suggested that α-lipoic acid improves insulin sensitivity in patients with type 2 diabetes mellitus [36,37]. However, we did not measure plasma insulin levels. Therefore, the changes of insulin sensitivity and its association to endothelial function during the intervention period could not be evaluated. It is worth noting that we did not find significant changes of FBG and 2-h BG during the α-lipoic acid intervention; we speculate that the short period of intervention may be responsible for this. Secondly, the number of study subjects is relatively small. It is difficult to exclude bias in the results, which should be confirmed in large studies. Thirdly, we did not evaluate the effect of oral α-lipoic acid on endothelial function in this study. Therefore, whether oral dosing of α-lipoic acid would have the same effect remains to be determined.

In conclusion, our data showed that IFG subjects have impaired endothelial function and that antioxidant α-lipoic acid can improve endothelial function through a decrease of oxygen-derived free radicals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2010.04.011.

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Review

Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy

Qian Xu [a], Jianhong Pan [b], Jingwen Yu [c], Xiaoxia Liu [a], Li Liu [a], Xialin Zuo [a], Ping Wu [a], Houliang Deng [a], Jingjing Zhang [a], Aimin Ji [a,*]

[a] Department of Pharmacy, Zhu-Jiang Hospital, Southern Medical University, Guangzhou, China
[b] Peking University Clinical Research Institute, Beijing, China
[c] Department of Endocrinology, People's Hospital of Hainan Province, Haikou, China

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ABSTRACT

Aims: To compare the efficacy and safety of daily lipoic acid (300–600 mg i.v.) plus methylcobalamin (500–1000 mg i.v. or im.) (LA–MC) with that of methylcobalamin alone (MC) on diabetic peripheral neuropathy (DPN).

Methods: Electronic database were searched for studies published up to November 1, 2012 and study quality was assessed in duplicate. A random or a fixed effect model was used to analyse outcomes which were expressed as risk ratios (RRs) or mean difference (MD). I^2 statistic was used to assess heterogeneity.

Results: Seventeen studies were included. Combined data from all studies showed that the LA–MC combination therapy was significantly superior to MC monotherapy (RR = 1.47; 95% CI: 1.37–1.58). Superiority of the LA–MC combination was shown in nerve conduction velocity (NCV) with WMDs of 6.89 (95% CI: 4.24–9.73) for median motor nerve conduction velocity (MNCV), 5.24 (4.14–6.34) for median sensory nerve conduction velocity (SNCV), 4.34 (3.03–5.64) for peroneal MNCV, and 4.53 (3.2–5.85) for peroneal SNCV. There were no serious adverse events associated with treatment.

Conclusions: The results of the meta-analysis show that treatment with LA–MC for 2–4 weeks is associated with better outcomes in NCV and neuropathic symptoms relative to MC treatment. However larger well-designed studies are required to confirm this conclusion.

Contents

* *Corresponding author at:* Department of Pharmaceutical, Zhujiang Hospital, Southern Medical University, 253 Industry Avenue, Guangzhou 510282, China. Tel.: +86 020 61643500; fax: +86 020 84300639.
E-mail addresses: xiaoqian7666@163.com (Q. Xu), aiminji@163.com (A. Ji).

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1. Introduction

Complications of diabetes mellitus (DM) include a variety of neuropathies. DPN is common and has been reported to be present in 12.3% of individuals at diagnosis increasing to up to 50% after 12 year of DM [1–3]. Characterized by chronic paraesthesia, and electrophysiological abnormalities, DPN has a dramatic negative effect on the patient's daily quality of life and function [1,4,5]. The pathogenetic mechanisms of DPN are diverse and not fully understood resulting in limitations to its treatment.

Lipoic acid (LA) was first used therapeutically in Germany to treat diabetic neuropathy and meta-analyses which have evaluated its efficacy and safety provide evidence that LA is a safe antioxidant which could be effective in treating diabetic neuropathy [6,7]. Methylcobalamin (MC) has also been widely used in the treatment of DPN [8,9] and a beneficial effect on nerve conduction has been reported. Recently, in Mainland China, several studies have assessed the efficacy and safety of LA–MC combination therapy compared with MC monotherapy in patients with DPN and have found that the former achieved significantly better results [1,2]. Because of the increasing interest in combination therapy, we conducted a meta-analysis of relevant RCTs which compared combination therapy and MC monotherapy.

2. Methods

2.1. Search strategy

We searched the electronic databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Data-base) without date or language restrictions. The key terms used in this search were (methylcobalamin or mecobalamin) and (lipoic acid or thioctic acid or alpha-lipoic acid) and (diabetic peripheral neuropathy or diabetic neuropathies).

2.2. Inclusion and exclusion criteria

We reviewed each article and retrieved articles based on the following inclusion criteria: (1) RCTs which compared efficacy and safety of LA–MC combination therapy vs. MC monotherapy in patients with DPN. (2) Treatment periods of 2–4 weeks for both groups. (3) Clinical therapeutic efficacy defined by changes in symptoms, tendon reflexes and NCV reported at the end of treatment. We excluded non-randomized trials and studies which administered oral supplements.

2.3. Data extraction

Reviewers screened the full texts from each article independently according to the search strategy. All potentially relevant data which met the inclusion/exclusion criteria were extracted independently by two of the reviewers (XU Q and PAN JH). Extracted data were compared to eliminate errors. Disagreement was solved by discussion and a consensus was finally reached.

2.4. Quality assessment

The methodological quality of included trials was assessed using an established Jadad scale (Table 1). The scores for each article ranged from 0 (lowest quality) to 7 (highest quality). Trials scoring 4–7 points represented good to excellent (high) quality and 0–3 points poor or low quality [10,11].

2.5. Data synthesis

Our meta-analysis was based on outcomes including clinical therapeutic efficacy and NCVs (median MNCV, median SNCV, peroneal MNCV, and peroneal SNCV) which were used in most of the studies as the primary outcomes. Clinical therapeutic efficacy was divided into three categories – markedly effective (disappearance of subjective symptoms, recovered tendon reflex, and NCV increased by at least 5 m/s), effective (alleviated subjective symptoms, improved tendon reflex, and NCV increased by at least 3 m/s) and ineffective (no improvement in symptoms, tendon reflex and NCV). Secondary outcomes, when available, were adverse events.

2.6. Statistical analysis

Dichotomous data are expressed as the risk ratio (RR) and continuous outcomes between groups as weighted mean difference (WMD), both with 95% confidence intervals (95% CI), using a fixed effect (FE) or randomized effect (RE) model for the studies. Z test was used to compare the overall WMD of combination group and the monotherapy group, and differences were considered to be statistically significant when

Table 1 – Methodology quality accessment – modified jadad score (7-point).

Items	Score standard		
	0	2	3
Randomization (A)	Not randomized or inappropriate method of randomization	The study was described randomized	The method of randomization was described and it was appropriate
Concealment of allocation (B)	Not describe the method of allocation concealment	The study was s described as using allocation concealment	The method of allocation concealment was described appropriately
Double blinding (C)	No blind or inappropriate method of blinding	The study was described as double blind	The method of double blinding was described and it was appropriate
Withdrawals and dropouts (D)	Not describe the follow-up	A description of withdrawal and dropout	

two-sided p-value was <0.05 or the 95% CI for RR exceeded 1.0 and WMD exceeded 0.1. Substantial heterogeneity [chi-squared test with degrees of freedom (d.f.)] was represented by I^2 of 50% or more. Significant difference for heterogeneity test was considered when $p < 0.01$. The meta-analysis was performed by RevMan5.0.25 software (Cochrane Collaboration, Oxford, UK) for the above statistical calculations. Publication bias was examined by funnel plots.

3. Results

3.1. Study description

We screened 198 citations and identified 17 studies for further analysis [12–28]. The quality assessment of the included studies is summarized in Table 1. The characteristics of included studies are summarized in Table 2. Most trials were not multicentered and the treatment courses ranged from 2 to 4 weeks. IV administration was commonly used. Many trials reported the number of patients with type 2 diabetes but some did not differentiate the number with type 1 or type 2 diabetes.

3.2. Efficacy

The results of fifteen trials with a total of 1106 patients were entered in our meta-analysis and demonstrated a significant difference in efficacy between LA–MC combination and MC monotherapy. We used the FE model for LA–MC vs. MC group because heterogeneity among the studies measured by the I^2 statistic chi^2 test was insignificant ($p = 0.92$, $I^2 = 0\%$). The combination was superior to monotherapy for efficacy ($p < 0.00001$, RR = 4.03, 95% CI = 1.37–1.58) (Fig. 1). The funnel shape was not absolutely symmetrical (Fig. 2), indicating a potential publication bias.

3.3. Nerve conduction velocities

At entry into the studies, the pooled analysis of NCVs taken as a continuous measurement showed no differences between

Table 2 – Study characteristics.

Source	Number (M + A)/M	Age A + M/M	Sex (men/women)	Treatment drugs sig/day			Study duration/days	Type of diabetes	Diabetes duration (year) A + M/M	Total score
				A + M		M				
				A	M					
Zhaoyy2008 [12]	75 (39/36)	54.5/55.3	38/37	600 ivgtt	500 im	500 im	21	2	9.2/9.2	4
Lihj2008 [15]	78 (39/39)	58.6/57.1	41/37	600 ivgtt	500 ivgtt	500 ivgtt	21	2	9.12/9.21	3
Zhangxl2009 [13]	60 (30/30)	58.8/59.0	34/26	500 ivgtt	500 ivgtt	500 ivgtt	21	2	NR	3
Suoln2009 [14]	64 (32/32)	65.0/65.0	38/36	600 ivgtt	500 ivgtt	500 iv	14	2	8.91/8.97	3
Zhangch2009 [16]	60 (32/28)	57.8/54.4	31/29	600 ivgtt	500 im	500 iv	21	NR	9.2/9.0	3
Xinyy2009 [17]	60 (30/30)	52.3/52.3	30/30	600 ivgtt	500 iv	500 iv	14	2	8.7/8.7	3
Jiazhm2010 [18]	80 (56/24)	48.0/48.0	46/34	600 ivgtt	500 im	500 iv	15	2	9.54/9.54	4
Zhaoyh2011 [19]	80 (40/40)	65.4/66.2	47/33	300 ivgtt	500 im	500 im	21	NR	8.3/8.3	3
Wangzhh2011 [20]	60 (32/28)	56/55.5	31/29	600 ivgtt	500 ivgtt	500 ivgtt	21	NR	9.8/9.7	3
Zhuyp2011 [21]	84 (42/42)	56.0/56.0	37/45	450 ivgtt	500 iv	500 iv	14	NR	9.8/10.0	3
Luosj2011 [22]	72 (38/34)	57.5/56.7	38/34	600 ivgtt	500 im	500 im	14	2	7.9/8.3	3
Songxc2011 [23]	84 (42/42)	57.0/62.0	39/45	600 ivgtt	500 ivgtt	500 ivgtt	14	2	NR	3
Gaoar2011 [24]	138 (46/46/46)	62.0/61.0	48/44	600 iv	500 iv	500 iv	14	NR	8.6/8.6	3
Linyl2012 [25]	102 (52/50)	50.6/51.8	39/63	600 ivgtt	500 iv	500 iv	14	NR	7.9/7.5	3
Yangy2012 [26]	86 (43/43)	55.7/55.7	52/34	600 iv	500 iv	500 iv	14	2	2.4/2.4	3
Cuify2012 [27]	65 (35/30)	41.2/41.6	38/27	450 ivgtt	500 iv	500 iv	28	2	NR	3
Zhangrq2012 [28]	60 (30/30)	65.8/65.9	36/24	600 ivgtt	1000 iv	1000 iv	21	2	8.5/8.5	3

Notes: A, lipoic acid; M, methylcobalamin; iv, intravenous; ivgtt, intravenous infusion; im, intramuscular; NR, not reported.

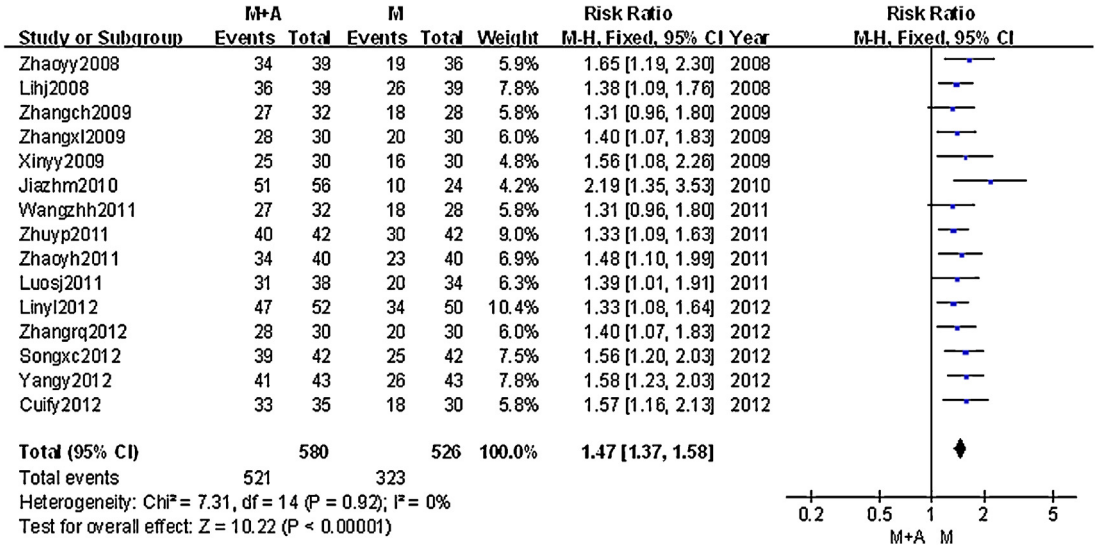

Fig. 1 – Comparison of efficacy of LA–MC group and MC alone group for DPN. *Notes*: A, lipoic acid; M, methylcobalamin.

the groups for any of the studies. After 2–4 weeks, the changes in NCVs differed significantly between the LA–MC combination and MC monotherapy groups (Fig. 3). Thirteen RCTs involving 1038 subjects reported median MNCV as an outcome. Significant between-studies heterogeneity was observed ($p < 0.00001$; $I^2 = 97\%$). The estimated WMD for LA–MC and MC monotherapy was 6.89 (95% CI: 4.24–9.73). For median SNCV, significant heterogeneity between studies was observed ($p < 0.00001$; $I^2 = 77\%$). There were 13 trials evaluating 978 patients showing a statistically significant effect in favour of LA–MC combination v MC monotherapy ($p < 0.00001$; MD = 5.24, 95% CI = 4.14–6.34). Fourteen trials with a total of 1058 patients reported peroneal MNCV as an outcome. Heterogeneity between trials was significant ($p < 0.00001$, $I^2 = 88\%$). Peroneal MNCV was statistically improved in the combination v monotherapy group ($p < 0.00001$, MD = 4.34, 95% CI = 3.03–5.64). For peroneal SNCV (12 trials $n = 918$), the result of heterogeneity between studies for the two groups was significant ($p < 0.00001$, $I^2 = 91\%$). The combination group was statistically superior to the MC group ($p < 0.0001$, OR = 4.53, 95% CI = 3.20–5.85).

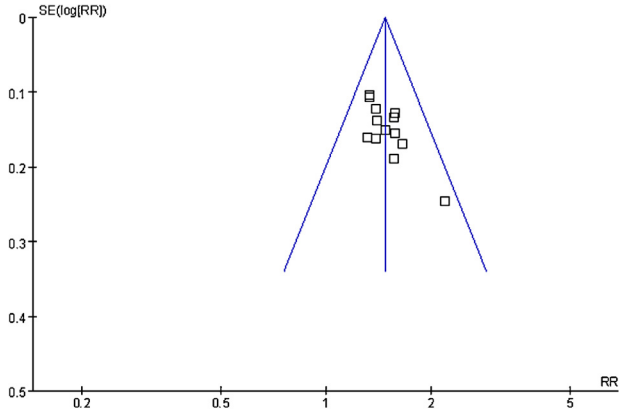

Fig. 2 – Funnel plot for LA–MC group vs. MC alone group for DPN.

3.4. *Adverse events*

Administration of LA at doses of 300–600 mg/day and MC at doses of 500–1000 μg/day intravenously for 2–4 weeks was well tolerated and no serious treatment-related adverse events were observed in the combination group. Only a few mild adverse effects such as mild swelling and pain at the injection site (5 cases) [17,28], headache (1 case) [23], nausea (1 case) [23] were reported in the combination group, and nausea (1 case) [23] in MC group. Because studies did not report these events in detail, we were unable to precisely compare rates of adverse events.

4. Discussion

Diabetes poses a growing burden in the world [29]. In the first decade of this century, the prevalence of DM among men and women in China has increased from 2.6% to 9.7% giving an estimated total of 92.4 million people with DM [30]. The Rochester Diabetic Neuropathy Study suggested that up to 65% of individuals with type 1 or type 2 diabetes have peripheral neuropathy [31]. The pathophysiology of diabetic neuropathy includes increased formation of advanced glycated end products, alterations in protein kinase C pathways [32], increased polyol pathway activity, decreased nitric oxide/impaired endothelial function [33], reduced (Na^+/K^+)-ATPase activity [34], and homocysteinemia [35].

The mechanisms of action of LA for the treatment of DPN may be related to improvements in nerve blood flow by means of anti-oxidation [36–38] and endothelial dysfunction by reducing levels of interleukin 6 and plasminogen activator 1 in plasma [39]. LA has also been reported to increase glucose uptake by nerve cells [40], (Na^+/K^+)-ATPase activity [41], and improve nitric oxide-mediated endothelium-dependent vasodilation [42]. Neuropathic symptoms, but not motor or sensory NCV, were improved by LA alone [6]. Han et al. reported that treatment with LA can improve NCVs, however, patients also

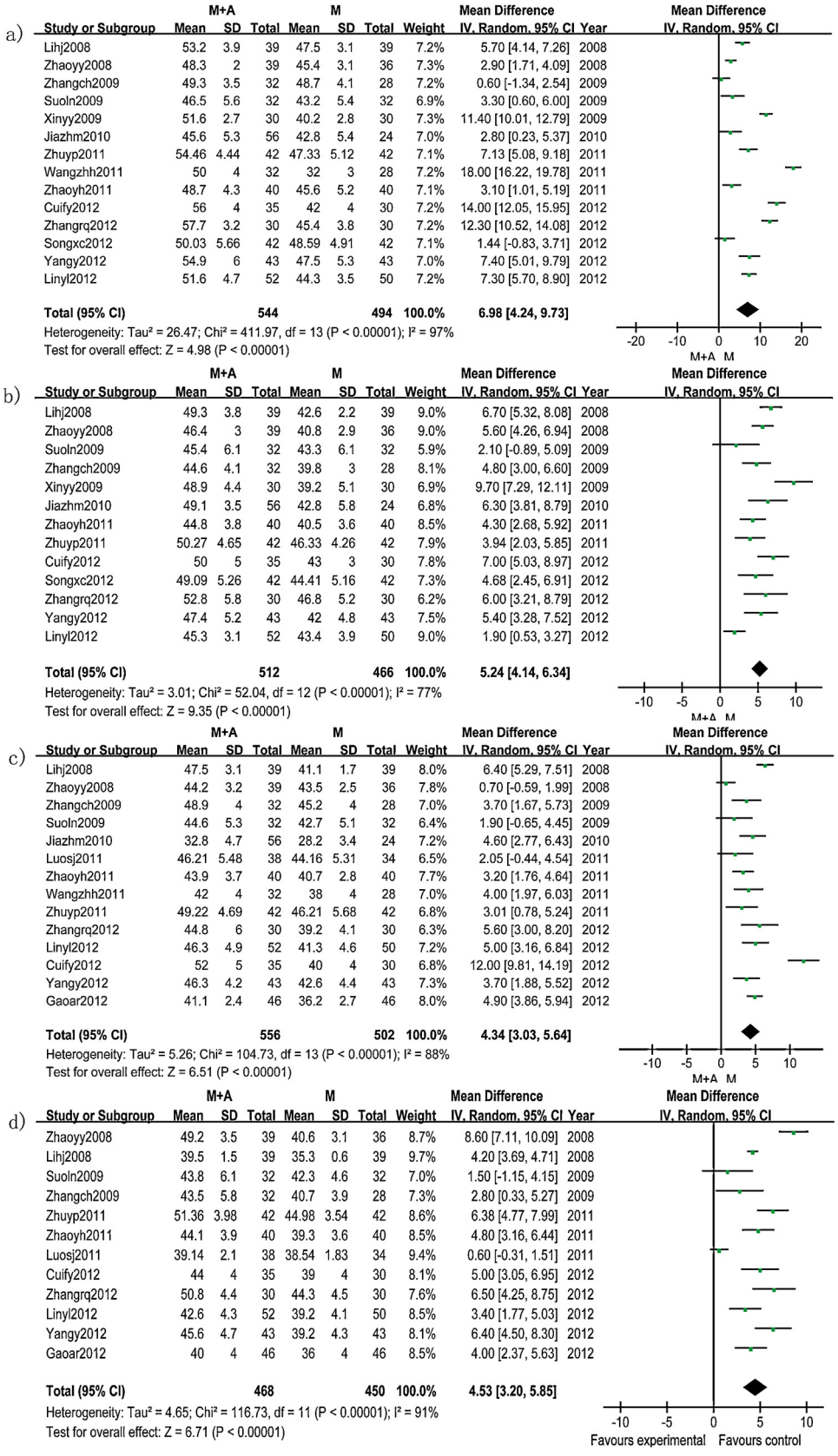

Fig. 3 – Comparison of NCVs, including (a) median MNCV; (b) median SNCV; (c) peroneal MNCV; and (d) peroneal SNCV, improvement of LA–MC group with MC alone group for DPN. *Notes*: A, lipoic acid; M, methylcobalamin.

received treatment with other drugs including MC or prostaglandin [7]. In short, studies suggest that using LA alone may not be sufficient to improve NCVs.

Studies with MC have reported beneficial effects and safety on recovery of peripheral nerve structure and function [8,43–45]. MC can directly accelerate transmethylation in nerve tissues, promote conversion of homocysteine to methionine, increase myelination, neuronal differentiation and replication, and increase biologic synthesis of phospholipids and nucleic acids. Mizukami et al. suggested that correction of impaired neural signal of protein kinase C and oxidative stress-induced damage may play a major role in the beneficial effects of MC on DPN [46].

There are several limitations of our meta-analysis that should be taken into account when interpreting the results. First, most of the studies included in this review had poor methodological quality. They were of small sample size and did not describe withdrawals or dropouts. Even if the study referred to the withdrawal or dropout, it did not explain whether they performed an intention-to-treat analysis. Second, no studies have yet assessed long-term effectiveness in terms of efficacy, harms and health outcomes.

In conclusion, although some limitations exist in this meta-analysis, treatment with LA (300–600 mg i.v.) plus MC (500–1000 mg i.v. or im.) once a day for 2–4 weeks resulted in better improvement in neuropathic symptoms and NCVs compared with administration of MC alone. Moreover, compared with MC alone, LA–MC combination therapy was not associated with more severe adverse events in patients with DPN. However due to poor methodological quality of the studies included in this meta-analysis, well-designed multicenter RCTs are required to confirm these findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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The authors have no relevant financial involvement with any organization with a financial interest in with the materials discussed in the manuscript. All authors conceived the study and developed the protocol.

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The College of Naturopaths of Ontario

APPLICATION TO AMEND THE SCHEDULE OF SUBSTANCES ESTABLISHED UNDER GENERAL REGULATION

Thank you for your interest in submitting an application to amend the schedule of substances established under General regulation of the College of Naturopaths. The College will review all completed applications.

Please complete all sections below and ensure that the information you provide on this form is current.

I. APPLICANT INFORMATION	
Name	Dr. Jonathan E. Prousky, ND, MSc, MA (on behalf of the CTC)
Company	Canadian College of Naturopathic Medicine
Address	1255 Sheppard Ave. East, North York, ON M2K 1E2
Phone Number(s)	416-498-1255 ext. 235
Email address	jprousky@ccnm.edu
II. DRUG/SUBSTANCE INFORMATION	
Drug/Substance Name (generic and trade where applicable)	Alpha Lipoic Acid/ Thioctic Acid (injection)
Is the drug/substance approved for use in Canada?	☒ Yes ☐ No
Is the drug/substance approved for use by NDs in British Columbia?	☒ Yes ☐ No
Was the drug/substance previously publicly available in Ontario and now restricted due to legislation?	☒ Yes ☐ No
Is it a controlled drug, as defined in *Controlled Drugs and Substances Act*?	☐ Yes ☒ No If Yes, which schedule? _____

If applicable, please indicate which NAPRA schedule applies to this drug/substance	☐ NAPRA Schedule I ☐ NAPRA Schedule II ☐ NAPRA Schedule III ☒ Unscheduled
Is the substance included on the Health Canada Prescription Drug List? Is the drug/substance restricted or requires a prescription due to dosage (i.e. requires prescription over a certain dose)?	☐ Yes ☒ No ☐ Yes ☒ No If Yes, please specify:
Is the substance a Natural Health Product as defined in the Natural Health Products Regulations?	☒ Yes ☐ No
III. **INDICATIONS AND CONTRAINDICATIONS**	
List disorders, disease, dysfunction treated:	1. Improves insulin-resistance and glucose disposal in type 2 diabetes 2. diabetic neuropathy, Peripheral neuropathy 3. Amanita mushroom poisoning 4. Orally-- for dementia, chronic fatigue 5. (Natural Medicines Database) …
Is the disease, disorder, dysfunction treated within the scope for Ontario NDs?	☒ Yes ☐ No
Is the drug/substance used for emergency situations?	☐ Yes ☒ No If Yes, what are the indications:

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Route of Administration	☐ Oral ☐ Topical ☐ Non-IV Injection. Route of Injection :_____ ☒ IV Injection ☐ Inhalation ☐ Other (please specify)_____
Indicate the dosage supported by the evidence, the duration of treatment and a dosing schedule	Adminstered intravenously in dosages no greater than 600 mg. Impaired glucose tolerance: 250mL of saline solution containing 600mg ALA. Ischemia-reperfusion injury protection: A dose of 600mg of alpha-lipoic acid in 50mL of sodium chloride. Type 2 diabetes: Alpha-lipoic acid 500-600mg in saline. (Natural Medicines Database)
Is the drug/substance required above allowable daily dosage? Include evidence supporting that the drug/substance is safe in the dosage used	☐ Yes ☒ No Mijnhout GS et al. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. Int J Endocrinol. 2012;2012:456279.
Provide any known potential contraindications or precautions for the drug/substance.	Hypersensitivity to alpha lipoic acid. No safety data on pregnancy and breastfeeding.
Does the profession have necessary tools to monitor the results? If No, list tools necessary for monitoring. (Where a laboratory or POCT is necessary, please attach the application)	☒ Yes ☐ No

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List all known or suspected adverse reactions for the drug/substance	Adverse events, including nausea, vomiting, and vertigo, have been reported in clinical trials but occur more frequently with alpha-lipoic acid doses of 600mg or more (mainly 1,200 and 1,800mg) Minimal side effects, including local pain during infusion and redness, have been reported with intravenous alpha-lipoic acid. (Natural Medicines Database)
List all known or suspected interactions with drugs/substances or natural health products	Moderate interaction with chemotherapy (level of evidence: D; might decrease effectiveness); thyroid hormone (level of evidence: D; reduces the conversion into active T3). Theoretically, alpha-lipoic acid might have additive effects with herbs that decrease blood glucose levels. Herbs with hypoglycemic potential include devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, and Siberian ginseng. (Natural Medicines Database)
Does the profession have necessary tools to manage adverse events? If No, list the tools necessary.	☒ Yes ☐ No
List all evidence, including source, date and level (See handbook.) *Please attach the evidence to your application.*	1. 1). Xu Q et al. Meta-analysis of methylcobalamin alone and in 2. combination with lipoic acid in patients with diabetic peripheral neuropathy.Diabetes Res Clin Pract. 2013 Aug;101(2):99-105.Level:A 3. 2). Grbovic V et al. Comparative analysis of the effects combined physical procedures and alpha-lipoic acid on the electroneurographic 4. parameters of patients with distal sensorimotor diabetic polyneuropathy.J Phys Ther Sci. 2016 Jan;28(2):432-7. Level: A 3). 5. Xiang G et al. α -Lipoic acid can improve endothelial dysfunction in … subjects with impaired fasting glucose. Metabolism. 2011 Apr;60 (4):480-5 Level: A. 4). Klugman A et al. Alpha lipoic acid for dementia (review). Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004244. Level: B. 5). Mijnhout GS et al. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. Int J Endocrinol. 2012;2012:456279.Level: A.

Please provide an explanation of how the drug/substance may be used in naturopathic practice, whether it is different from allopathic use, what is the impact of the drug/substance on the patient care and whether the profession possesses the knowledge, skills and judgement to administer the drug/substance.

According to Xu et al (2013), alpha lipoic acid was first used therapeutically in Germany to treat diabetic neuropathy. There are a number of studies showing its efficacy in treating peripheral neuropathy. A meta-analysis by Mijnhout (2012) found that ALA 600 mg IV once a day for 3 weeks had significant and clinically relevant reduction in neuropathic pain. Xu (2013) found that 300-600 mg IV of ALA plus methylcobalamin (500-1000 mg IV or IM) once a day for 2-4 weeks resulted in neuropathy improvement compared to methylcobalamin alone. In a study by Grbovic (2016) patients with diabetic neuropathy were treated with ALA 600 mg in 500 ml of 0.9% NaCl once a day for 12 days, then ALA 600 mg/d per orem. They showed statistically significant improvements in nerve conduction studies. A study by Xiang et al (2011) found that ALA 600 mg IV infusion once a day for 3 weeks improved endothelial function by decreasing oxygen free radicals in patients with impaired fasting glucose.

The use of ALA IV in naturopathic practice would be similar to its allopathic use. It will positively impact patient care by improving patient symptoms subjectively and objectively (through nerve conduction studies). The profession possesses the knowledge, skills, and judgment to administer this medication in practice.

Level of evidence: A

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Review Article

Alpha Lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials

Gerritje S. Mijnhout,[1] Boudewijn J. Kollen,[2] Alaa Alkhalaf,[1,3,4] Nanno Kleefstra,[3,4,5] and Henk J. G. Bilo[1,3,4]

[1] *Department of Internal Medicine, Isala Clinics, P.O. Box 10400, 8000 GK Zwolle, The Netherlands*
[2] *Department of General Practice, University Medical Centre Groningen, University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands*
[3] *Department of Internal Medicine, University Medical Centre Groningen, University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands*
[4] *Diabetes Centre, Isala Clinics, P.O. Box 10400, 8000 GK Zwolle, The Netherlands*
[5] *Langerhans Medical Research Group, P.O. Box 21, 4254 ZG Sleeuwijk, The Netherlands*

Correspondence should be addressed to Gerritje S. Mijnhout, g.s.mijnhout@isala.nl

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Objective. We performed a systematic review of the literature to evaluate the effects of alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes mellitus. *Research design and methods*. The databases MEDLINE and EMBASE were searched using the key words "lipoic acid", "thioctic acid", "diabet*", and the MeSH-terms "thioctic acid" and "diabetes mellitus". Randomised controlled trials using the TSS score as the outcome measure were selected and assessed for their methodological quality. Study selection and quality assessment were performed independently by three observers. *Results*. Overall, the pooled standardized mean difference estimated from all trials revealed a reduction in TSS scores of −2.26 (CI: −3.12 to −1.41; $P = 0.00001$) in favour of alpha lipoic acid administration. Subgroup analyses of oral administration (−1.78 CI: −2.45 to −1.10; $P = 0.00001$) and intravenous administration (−2.81 CI: −4.16 to −1.46; $P = 0.0001$) confirmed the robustness of the overall result. *Conclusions*. When given intravenously at a dosage of 600 mg/day over a period of 3 weeks, alpha lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain (grade of recommendation A). It is unclear if the significant improvements seen after 3–5 weeks of oral administration at a dosage of ≥600 mg/day are clinically relevant.

1. Introduction

Neuropathy is a microvascular complication of diabetes mellitus which leads to considerable morbidity and a decreased quality of life [1]. Peripheral neuropathy can present as tingling, burning, pain, cramps, paresthesia, or numbness. There is overwhelming evidence that the development of microvascular complications is related to the level of glucose dysregulation over a long period of time [2]. Hyperglycaemia induces an increased production of free oxygen radicals in the mitochondria (oxidative stress), which leads to the activation of the four known pathways that are responsible for hyperglycaemic damage: the polyol, hexosamine, protein kinase C, and AGE pathways [3]. This results in damage of endothelial and neuronal cells.

Neuropathic pain is difficult to treat, and standard analgesics are usually not effective enough [4]. The medications which are currently used to treat neuropathic pain in patients with diabetes include mainly antidepressants, antiepileptics, and opioids. These medications are limited in their effectiveness, they have considerable side effects, and they have no effect on the processes by which hyperglycaemia leads to cell damage [5]. Antioxidants, such as alpha lipoic acid, could theoretically be effective in treating diabetic neuropathy. In

Table 1: Methodological quality assessment of the included intervention studies.

		Ziegler 1995 [15] ALADIN	Ruhnau 1999 [16] ORPIL	Ametov 2003 [17] SYDNEY	Ziegler 2006 [18] SYDNEY 2
(1)	Randomisation?	yes	yes	yes	yes
(2)	Concealment of allocation?	yes	yes	yes	yes
(3)	Patients blinded?	yes	yes	yes	yes
(4)	Doctors blinded?	yes	yes	yes	yes
(5)	Investigators blinded?	NO	NO	NO	NO
(6)	Groups comparable at baseline?	yes	yes	yes	yes
(7)	Follow-up complete of >80% of patients?	yes	yes	yes	yes
(8)	Intention-to-treat analysis?	yes	yes	yes	yes
	Level of evidence	1b	1b	1b	1b

1951, alpha lipoic acid was identified as a coenzyme in the tricarboxylic acid cycle (Krebs Cycle) [6]. Alpha lipoic acid is also a potent antioxidant, reported to reduce and prevent diabetic micro- and macrovascular complications in animal models [7, 8]. A recent study in humans with type 1 diabetes mellitus showed a normalisation of the increased AGE formation and a reduction of the hexosamine pathway [9]. By preventing the damage caused by hyperglycaemia, alpha lipoic acid may not only be an analgesic treatment but may also improve nerve function. In addition, recent evidence shows that alpha lipoic acid decreases neuronal sensitivity to pain by selectively inhibiting neuronal T-type calcium channels [10]. Moreover, compared to the medications currently in use, alpha lipoic acid has few side effects [11]. In Germany, alpha lipoic acid is approved for the treatment of diabetic neuropathic pain and covered by health insurance companies, but use has not been widely adopted elsewhere.

An earlier meta-analysis of four randomized controlled trials (RCTs) on alpha lipoic acid (600 mg/day) in patients with diabetes and neuropathic pain concluded that three weeks of treatment with intravenous alpha lipoic acid (600 mg/day) led to a significant decrease in reported neuropathic pain [12]. However, studies investigating the effect of oral administration were not included. In addition, the meta-analysis did not fulfil the Cochrane methodological criteria for systematic reviews. A protocol for a proposed systematic review can be found in the Cochrane Library [13]. Recently, we performed a qualitative systematic review of the literature [14]. In addition, it was our purpose to extend the literature search and to perform a quantitative meta-analysis. The aim of this meta-analysis was to evaluate the effects of intravenous as well as oral administration of alpha lipoic acid versus placebo in patients with symptomatic peripheral diabetic neuropathy.

2. Research Design and Methods

2.1. Literature Search. In November 2010, three of the authors (GSM, AA, and NK) conducted a search for relevant publications in the electronic database MEDLINE, using the search engine *PubMed*, and EMBASE. The search strategy used in MEDLINE used the terms "lipoic acid", "thioctic acid", and "diabet*" and the MeSH terms "thioctic acid" and "diabetes mellitus": (((lipoic acid OR thioctic acid OR thioctic acid [MeSH]) AND (diabete* OR diabeti* OR diabeto* OR diabetes mellitus [MeSH])) AND ((clinical [Title/Abstract] AND trial [Title/Abstract]) OR clinical trials [MeSH Terms] OR clinical trial [Publication Type] OR random* [Title/Abstract] OR random allocation [MeSH Terms] OR therapeutic use [MeSH Subheading])). A similar search strategy was used in EMBASE: ((lipoic acid OR thioctic acid) AND (diabetes mellitus OR diabetic*) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)). All authors obtained the same results.

2.2. Study Selection. For study selection, the following inclusion criteria were used: (1) RCTs on alpha lipoic acid, (2) a study population consisting of patients with diabetes mellitus and peripheral neuropathic pain, and (3) use of the total symptom score (TSS) as the outcome measure. Language was not a restriction. GSM, AA, and NK independently identified studies to be included in the review by checking the titles and abstracts downloaded from the databases. A consensus meeting was then held to resolve any disagreements. The final decision to include or exclude any study was based on the article's full text. The reference lists of the identified studies were reviewed to discover additional potentially eligible studies. Unpublished data and conference proceedings were excluded from this review.

2.3. Methodologic Quality Assessment. The aforementioned authors proceeded to independently evaluate the quality of each study using the standardised evaluation form for RCTs and systematic reviews developed by the Dutch Cochrane Centre (http://www.cochrane.nl/) (Table 1). Levels of evidence and recommendation grades were applied according to the Oxford Centre of Evidence-based Medicine, version 2001 (http://www.cebm.net/index.aspx?o=1025/).

Table 2: Total Symptom Score (TSS): scoring system for neuropathic symptoms (pain, burning, paresthesia, and numbness). The score can range from 0 (no symptoms) to maximally 14.64 (all symptoms present, severe, continuous).

Symptom frequency	Symptom intensity			
	Absent	Slight	Moderate	Severe
Occasional	0	1.00	2.00	3.00
Frequent	0	1.33	2.33	3.33
(Almost) continuous	0	1.66	2.66	3.66

2.4. Outcome Measure. The primary outcome measure in this meta-analysis was the total symptom score (TSS). The TSS is a questionnaire in which the patient is asked to assess the intensity (absent, mild, moderate, severe) and the frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness) resulting in a scaled score in which 0 means no symptoms and 14.64 means that all four symptoms are severe and more or less continuously present (Table 2). A 30% change on this scale is considered to be clinically relevant (or ≥2 points in patients with a starting score ≤4 points) [15].

2.5. Statistical Analysis. For the purpose of this meta-analysis, overall results based on TSS scores were combined for oral and intravenous administration of alpha lipoic acid and placebo. Meta-analysis was undertaken using RevMan5 software (The Nordic Cochrane Centre, The Cochrane Collaboration). The I^2 statistic was used to assess statistical heterogeneity [19]. An $I^2 > 30\%$ was considered to denote heterogeneity. A random-effect model was used in case of heterogeneity, a fixed-effect model in the absence of heterogeneity. The inverse-variance method was used to weigh the scores of individual studies. When possible, study authors were contacted to clarify data. Studies were excluded from the meta-analysis if insufficient information was provided to enable standard error calculation. The Mantel–Haenszel method was subsequently applied to estimate pooled effect sizes. In order to explore the robustness of our results we conducted the following, a priori specified, subgroup analyses: intravenous and oral administration of alpha lipoic acid versus placebo.

We adhered to the QUOROM guidelines for the reporting of meta-analyses of randomised trials [20].

3. Results

3.1. Identification and Selection of Studies. The search yielded 242 publications in Medline and 112 in Embase (Figure 1). The 112 publications found in Embase were also identified in Medline. After reviewing the titles and the abstracts of the 242 publications, 10 randomised placebo-controlled trials on alpha lipoic acid in patients with diabetic neuropathic pain were selected [15–18, 21–26]. After reading the complete articles, two studies were excluded [21, 22], because they dealt with the effects of alpha lipoic acid on autonomic instead of diabetic neuropathy. Two studies [23, 24] were excluded because the TSS was not used as an outcome measure. There was no disagreement among the reviewers regarding the studies selected for inclusion.

3.2. Methodological Quality Assessment. A survey of the methodological quality assessment is shown in Table 1. Four of the RCTs [15–18] were of good methodological quality (level 1b). Two RCTs [25, 26] had substantial methodological limitations (level 2b). The study of Liu et al. [26] was excluded from our meta-analysis because of unacceptable methodological limitations, including absence of allocation concealment and blinding. The study of Ziegler et al. [25] was considered for inclusion despite exclusion bias due to selective loss to follow-up, but the article provided insufficient information to enable standard error calculation. The study authors were contacted to clarify data, but they did not respond to repeated requests. Therefore, also this study was excluded from the meta-analysis.

3.3. Descriptive Analyses of Selected Randomized Controlled Trials. Finally, four RCTs were included in our systematic review and meta-analysis. The study populations in the four selected RCTs were all made up of patients with peripheral diabetic neuropathy [15–18]. The age range was from 18 to 74 years, and most of the patients included had type 2 diabetes mellitus. The effects of orally administered alpha lipoic acid were investigated in two studies and intravenous administration in another two studies (Table 3). Two studies incorporated multiple dose comparisons. The dosage of alpha lipoic acid ranged from 100 to 1800 mg per day. Intravenous alpha lipoic acid was given for three weeks, and oral administration varied between three weeks and six months.

A significant improvement in the TSS scores was reported in all studies. In these studies an average 50% reduction was seen in the TSS with the oral or intravenous administration of at least 600 mg per day. However, when compared to the subjects in the control groups, the reduction in TSS was actually less than the clinically relevant threshold of 30% [15], as the TSS in the control group also decreased. This was particularly evident in the studies where alpha lipoic acid was administered orally. In one study, in which the alpha lipoic acid was administered intravenously, the intervention group did show a more than 30% reduction in TSS when compared to the control group [16]. Dosages higher than 600 mg per day did not result in a further improvement in the TSS and resulted in a greater incidence of side effects such as nausea, vomiting, and dizziness. The side effects seen with dosages ≤600 mg per day were not different than seen with placebo. A safety analysis of treatment with alpha lipoic acid over 4 years in diabetic polyneuropathy [27] showed that treatment tolerability and discontinuations due to lack of tolerability did not differ between placebo and treatment groups. However, the rates of serious adverse events were higher on alpha lipoic acid (38.1%) than those on placebo (28.0%) [27]. Of all reported adverse events, only heart rate and rhythm disorders were observed significantly more frequently in patients treated with alpha lipoic acid compared to patient treated with placebo (6.9% versus 2.7%, P 0.047) [27].

Table 3: Overview of the included randomized, placebo-controlled studies with alpha lipoic acid in persons with symptomatic peripheral diabetic neuropathy.

Study 1st author, year; study name	Research group		Length of study	Alpha lipoic acid dosage	Administration route	Primary outcome measure	Findings		Difference intervention versus control* (Significance)	level of evidence
	Patient type	Number of patients (Intervention/control)					Intervention	Control		
Ziegler 1995 ALADIN [15]	DM2; 18–70 yr	328 (65/63/66/66)	3 weeks	(a) 100 mg daily (b) 600 mg daily (c) 1200 mg daily	Intravenous	TSS	(a) 7.6 → 4.3 (b) 7.8 → 2.8 (c) 7.6 → 3.1	6.8 → 4.2	−0.7 (ns) −2.4 ($P < 0.001$) −1.9 ($P = 0.003$)	1b
Ruhnau 1999 ORPIL [16]	DM2; 18–70 yr	24 (12/12)	3 weeks	3dd600 mg	Oral	TSS	7.99 → 4.24	8.18 → 6.24	−1.81 ($P = 0.021$)	1b
Ametov 2003 SYDNEY [17]	DM1+ DM2; 18–74 yr	120 (60/60)	3 weeks	600 mg daily for 14 days	Intravenous	TSS	−5.72	−1.83	−3.89 ($P < 0.001$)	1b
Ziegler 2006 SYDNEY 2 [18]	DM1+ DM2; 18–74 yr	181 (45/47/46 /43)	5 weeks	(a) 600 mg daily (b) 1200 mg daily (c) 1800 mg daily	Oral	TSS	(a) 9.44 → 4.59 (b) 9.40 → 4.90 (c) 9.02 → 4.32	9.27 → 6.35	−1.93 ($P < 0.05$) −1.58 ($P < 0.05$) −1.78 ($P < 0.05$)	1b

* Calculated differences between intervention and control groups: not controlled.
DM: diabetes mellitus.
ns: not significant.
TSS: Total Symptom Score.

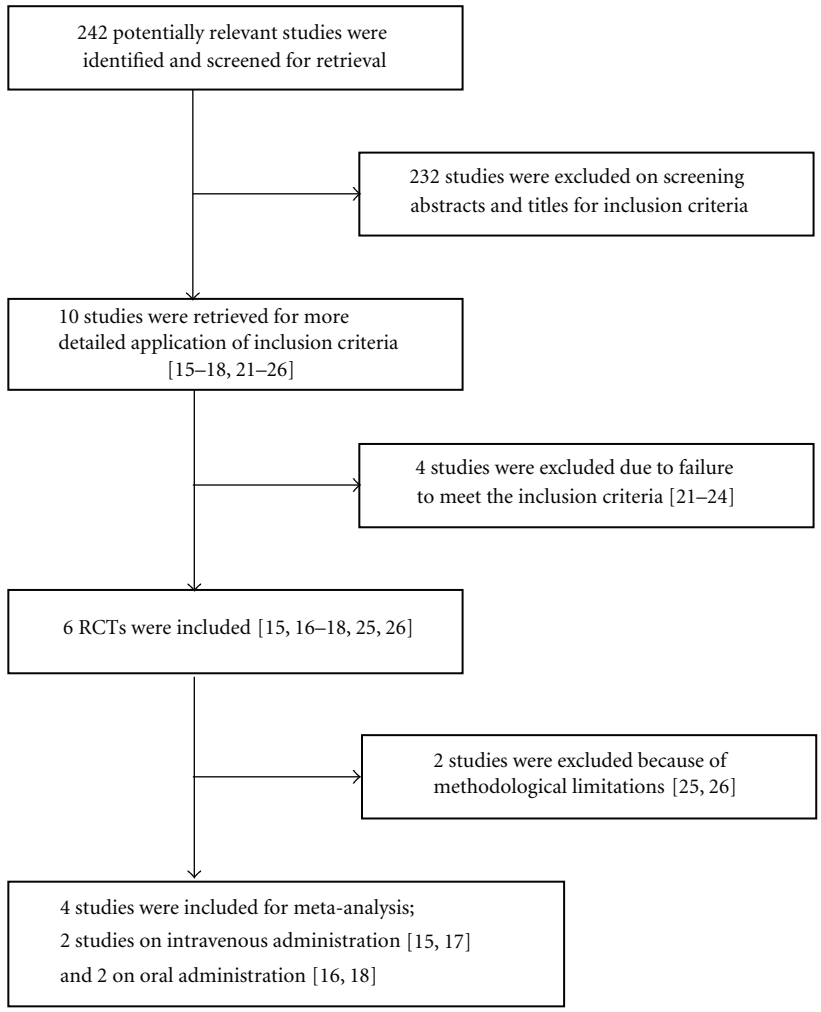

Figure 1: Flow diagram.

3.4. Meta-Analysis. Overall, the pooled standardized mean difference estimated from all trials revealed a reduction in TSS scores of −2.26 (CI: −3.12 to −1.41; $P = 0.00001$) in favour of alpha lipoic acid administration (Table 4). The outcome of the subgroup analyses of oral administration (−1.78 CI: −2.45 to −1.10; $P = 0.00001$) and intravenous administration (−2.81 CI: −4.16 to −1.46; $P = 0.0001$) confirmed the robustness of the overall result (Tables 5 and 6).

4. Discussion

Based on the four level 1b randomized, placebo-controlled studies included here, there is evidence to support that alpha lipoic acid causes a significant and clinically relevant decrease in neuropathic pain when administered for a period of three weeks at a dosage of 600 mg per day (grade of recommendation A). However, the significant improvements seen after the oral administration of alpha lipoic acid over a period of 3–5 weeks at a dosage of ≥600 mg per day are probably not clinically relevant, because the reduction in TSS was actually less than the threshold of 30% considered to be clinically relevant. There are, at present, no publications in which the effects of long-term treatment with intravenous or oral lipoic acid are presented.

The RCTs are primarily performed by a single German research group. A number of these studies were multicenter studies which included German as well as Russian, Israeli, and Croatian patients. Presumably, there is no overlap between these patient populations. All studies were sponsored by a pharmaceutical company which manufactured alpha lipoic acid. A number of the authors received salaries from this company, besides which, the pharmaceutical company also had representatives sitting on the advisory body for several of these studies.

It is striking that clinically relevant effects on neuropathic pain are seen after only 3–5 weeks of alpha lipoic acid administration. This is unexpectedly rapid for an antioxidising diet supplement. This may be explained by the selective modulation of neuronal T-type calcium channels by alpha lipoic acid [10]. In studies on diabetic autonomic neuropathy, effects of alpha lipoic acid were seen after 8–16 weeks [21, 22], depending on the study design.

Table 4: Standardized mean differences for the administration of orally and intravenously administered alpha-lipoic acid versus placebo in the treatment of neuropathic pain. Diamond denotes pooled estimate of overall effect. Weighing of individual studies is based on the inverse variance method. For subgroups, see Table 3.

Study or subgroup	Alpha-lipoic acid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Ametov et al. 2003	−5.72	1.53	60	−1.83	1.97	60	18.1%	−3.89 (−4.52, −3.26)	
Ruhnau et al. 1999	−3.75	1.88	12	−1.94	1.5	12	13.3%	−1.81 (−3.17, −0.45)	
Ziegler et al.1995b	−5	4.1	63	−2.6	3.2	66	13.9%	−2.40 (−3.67, −1.13)	
Ziegler et al. 1995c	−4.5	3.7	66	−2.6	3.2	66	14.5%	−1.90 (−3.08, −0.72)	
Ziegler et al. 2006a	−4.85	3.03	45	−2.92	3.18	43	13.7%	−1.93 (−3.23, −0.63)	
Ziegler et al. 2006b	−4.5	3.28	47	−2.92	3.18	43	13.5%	−1.58 (−2.92, −0.24)	
Ziegler et al. 2006c	−4.7	3.54	46	−2.92	3.18	43	13.1%	−1.78 (−3.18, −0.38)	
Total (95% CI)			**339**			**333**	**100%**	**−2.26 (−3.12, −1.41)**	

Heterogeneity: $\tau^2 = 0.95$; $\chi^2 = 22.98$, $df = 6$ ($P = 0.0008$); $I^2 = 74\%$

Test for over all effect: $Z = 5.19$ ($P < 0.00001$)

−4 −2 0 2 4

Favours alpha-lipoid acid Favours placebo

Table 5: Standardized mean differences for the administration of intravenously administered alpha-lipoic acid versus placebo in the treatment of neuropathic pain. Diamond denotes pooled estimate of overall effect. Weighing of individual studies is based on the inverse variance method. For subgroups, see Table 3.

Study or subgroup	Alpha-lipoic acid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Ametov et al. 2003	−5.72	1.53	60	−1.83	1.97	60	38.1%	−3.89 (−4.52, −3.26)	
Ziegler et al. 1995b	−5	4.1	63	−2.6	3.2	66	30.4%	−2.40 (−3.67, −1.13)	
Ziegler et al. 1995c	−4.5	3.7	66	−2.6	3.2	66	31.6%	−1.90 (−3.08, −0.72)	
Total (95% CI)			**189**			**192**	**100%**	**−2.81 (−4.16, −1.46)**	

Heterogeneity: $\tau^2 = 1.14$; $\chi^2 = 10.68$, $df = 2$ ($P = 0.005$); $I^2 = 81\%$

Test for over all effect: $Z = 4.07$ ($P < 0.0001$)

−4 −2 0 2 4

Favours alpha-lipoid acid Favours placebo

Table 6: Standardized mean differences for the administration of orally administered alpha-lipoic acid versus placebo in the treatment of neuropathic pain. Diamond denotes pooled estimate of overall effect. Weighing of individual studies is based on the inverse variance method. For subgroups, see Table 3.

Study or subgroup	Alpha-lipoic acid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, fixed, 95% CI	Mean difference IV, fixed, 95% CI
Ruhnau et al. 1999	−3.75	1.88	12	−1.94	1.5	12	24.5%	−1.81 (−3.17, −0.45)	
Ziegler et al. 2006a	−4.85	3.03	45	−2.92	3.18	43	26.9%	−1.93 (−3.23, −0.63)	
Ziegler et al. 2006b	−4.5	3.28	47	−2.92	3.18	43	25.4%	−1.58 (−2.92, −0.24)	
Ziegler et al. 2006c	−4.7	3.54	46	−2.92	3.18	43	23.2%	−1.78 (−3.18, −0.38)	
Total (95% CI)			**150**			**141**	**100.0%**	**−1.78 (−2.45, −1.10)**	

Heterogeneity: $\chi^2 = 0.14$, $df = 3$ ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 5.17$ ($P < 0.00001$)

−4 −2 0 2 4

Favours alpha-lipoid acid Favours placebo

The included RCTs were not designed for neuropathic pain. Individual scores on each of the four symptoms of the TSS (pain, burning, paresthesia, numbness) were not available from the included studies.

Unfortunately, there are not yet any results published for its administration over a longer time period. The continued, long-term effectiveness of any treatment is of the utmost importance for chronic conditions such as diabetic neuropathy.

In The Netherlands, the cost of using alpha lipoic acid at a dosage of 600 mg per day varies between 17.15 and 75.00 euros per month, depending on the manufacturer [14]. In comparison, the costs of amitriptyline, carbamazepine, duloxetine, gabapentin, and pregabalin are, respectively, 3.41, 9.38, 35.80, 53.75, and 71.71 euros per month (based on the Z-index tax, 2010) [28].

Finally, a meta-analysis is likely to suffer from publication bias, methodological deficiencies, and heterogeneity. We kept

the likelihood of bias to a minimum by developing a detailed protocol before starting this study, undertaking a meticulous search for published studies, and using explicit methods for study selection, data extraction, and data analysis. Also, we studied the totality of the randomized evidence by including all relevant properly randomized trials.

We conclude that intravenous administration of alpha lipoic acid leads to significant and clinically relevant improvements of symptomatic peripheral diabetic neuropathy in the short term. The results we present are encouraging enough to consider intravenous alpha lipoic acid for the treatment of diabetic neuropathy in patients, who do not respond to common therapy. It is unclear if the significant improvements seen with the oral administration of alpha lipoic acid are clinically relevant. Additional research of longer duration using an informative neuropathic pain scale will be necessary to investigate the effects of both routes.

Authors' Contribution

G. S. Mijnhout developed the search strategy, performed database search and selection of studies and the methodological quality assessment, and wrote the manuscript; B. J. Kollen was responsible for the statistical methodology of study, performed statistical pooling, and edited the manuscript; A. Alkhalaf and N. Kleefstra performed database search, selection of studies, and methodological quality assessment and edited the manuscript; H. J. G. Bilo edited the manuscript and was responsible for critical appraisal and final approval of the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interest to disclose.

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Original Article

Comparative analysis of the effects combined physical procedures and alpha-lipoic acid on the electroneurographic parameters of patients with distal sensorimotor diabetic polyneuropathy

Vesna Grbovic[1)], Aleksandra Jurisic-Skevin[1, 2)], Svetlana Djukic[2)], Srdjan Stefanović[2)], Jasmin Nurkovic[1, 3)*]

[1)] *Center for Physical Medicine and Rehabilitation, Clinical Center Kragujevac: 30 Zmaj Jovina Street, 34000 Kragujevac, Serbia*
[2)] *Faculty of Medical Sciences, University of Kragujevac, Serbia*
[3)] *Department of Biomedical Sciences, State University of Novi Pazar, Serbia*

Abstract. [Purpose] Painful diabetic polyneuropathy occurs as a complication in 16% of all patients with diabetes mellitus. [Subjects and Methods] A clinical, prospective open-label randomized intervention study was conducted of 60 adult patients, with distal sensorimotor diabetic neuropathy two groups of 30 patients, with diabetes mellitus type 2 with distal sensorimotor diabetic neuropathy. Patients in group A were treated with combined physical procedures, and patients in group B were treated with alpha lipoic acid. [Results] There where a statistically significant improvements in terminal latency and the amplitude of the action potential in group A patients, while group B patients showed a statistically significant improvements in conduction velocity and terminal latency of n. peroneus. Group A patients showed a statistically significant improvements in conduction velocity and terminal latency, while group B patients also showed a statistically significant improvements in conduction velocity and terminal latency. This was reflected in a significant improvements in electrophysiological parameters (conduction velocity, amplitude and latency) of the motor and sensory nerves (n. peroneus, n. suralis). [Conclusion] These results present further evidence justifying of the use of physical agents in the treatment of diabetic sensorimotor polyneuropathy.
Key words: Diabetic polyneuropathy, Physical procedures

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INTRODUCTION

Painful diabetic polyneuropathy occurs as a complication in 16% of all patients with diabetes mellitus[1)]. The prevalence in patients suffering from diabetic polyneuropathy varies from 23 to 29%[2)]. The presence of neurological symptoms and/or signs in electroneurographic (ENG) findings is necessary for confirming the diagnosis of distal sensorimotor diabetic polyneuropathy (DSMP)[3, 4)]. Slow sensitivity and motor velocity of conduction exists in clinically evident neuropathy, especially in the feet, where the peripheral nerves are the longest. The degree of deceleration of velocity conduction is proportional to the severity of the underlying disease[5)].

While drug therapy has been widely researched into and is quite well defined in the treatment of diabetic neuropathy, this is not the case with physical procedures. Physical therapy for the treatment of patients with distal sensorimotor polyneuropathy has increasingly been gaining in importance, especially as an analgesic therapy. Furthermore, in previous studies have neither researched the effects of combined physical therapy on electro-diagnostic parameters, nor made comparisons the effects

*Corresponding author. Jasmin Nurkovic (E-mail: jnurkovic@gmail.com)

of the alpha lipoic acid. Therapies directed at the pathogenesis process of diabetic neuropathies comprise aldose reductase inhibitors, alpha-lipoic acid, benfotiamine, protein kinase C inhibitors, gene therapy, gamma-linoleic acid, immunotherapy, and others[6].

Alpha-lipoic acid is an antioxidant that is endogenously produced in the body and has become studies the drug of choice for the treatment of diabetic neuropathy[7, 8]. It is particularly important to emphasize the necessity of prompt therapy, before the occurrence of severe and irreversible changes in the nerves. Alpha-lipoic acid has a clear metabolic effect, improves microcirculation, and has an anti-inflammatory effect. All these facts act synergistically and complexly in a chain of pathophysiological processes in the development of the diabetic neuropathies[8, 9].

The most commonly applied physical agents are transcutaneous electrical nerve stimulation (TENS), impulse magnetic field, stable galvanization and exercise. TENS is a method of treating the symptoms of pain by stimulating the sensitive nerve endings in the skin. It the modulations the pain at the dorsal horn of the spinal cord, and is based on the theory of control of pain inputs (the gate control theory of pain)[10–12]. Galvanic current causes hyperemia of the skin and deeper tissues through which it passes and reduces pain. Hyperemia improves trophic tissue, reduces swelling and inflammation and helps to alleviate the factors that induce pain[13]. Physical activity is beneficial for the metabolic processes in the body of diabetic patients and is implemented as a permanent therapeutic measure (it increases the biological effectiveness of insulin, sensitivity of insulin receptors, collateral circulation and the transport of oxygen, it lowers levels of triglycerides, cholesterol and blood pressure)[12].

Clinical studies have so far investigated the effects of certain modalities of physical therapy and alpha-lipoic acid in patients with various causes and types of neuropathies[13, 14]. However, the available literature has no data on comparative, randomized studies of the effects of physical therapy and alpha lipoic acid in patients with sensory neuropathy, especially in the subgroup of patients with diabetes mellitus. Bearing in mind the significant differences between the two therapeutic strategies in terms of clinical-management and economic aspects, there is an interest in comparative studies in this field. Thus, the main objective of our research was to investigate the effect of the application of combined physical procedures to electromyoneurographic (EMNG) parameters of peripheral sensory and motor nerves (n. peroneus and n. suralis) and compare it with the effect of treatment with alpha-lipoic acid in patients with distal sensorimotor polyneuropathy.

SUBJECTS AND METHODS

A clinical, prospective open-label randomized intervention study was conducted of 60 adult (18 years or older) who were patients at the Clinical Center, Kragujevac, Center for Physical Medicine and Rehabilitation during 2012-2013. The study was approved by the Ethics Committee of the Clinical Center, Kragujevac.

The inclusion criteria of the study were: patients with DSMP for longer than two months diagnosed with the presence of signs and symptoms (pain, paresthesia, hyperesthesia to anesthesia, muscular weakness) and EMNG findings; treatment with antidiabetic therapy which had not been changed for at least 6 months; and a signed, voluntary consent to participation in the study.

The exclusion criteria were: vitamin B12 deficiency, alcoholism, chronic renal insufficiency, thyroid dysfunction, immunodeficiency, systemic connective tissue disease, severe liver damage, cerebrovascular ischemia, cardiac decompensation, acute coronary syndrome in the previous 6 months, unregulated elevated blood pressure (>160/80 mmHg), treatment with chemotherapy in the last 10 years, state after severe polytrauma, as well as use of drugs that can damage the peripheral nerves (vincristine, paclitaxel, cisplatin, streptomycin, isoniazid, ethionamide, dapsone, nitrofurantoin, metronidazole, emetine, chloroquine, amiodarone, carbamazepine, phenytoin, hydralazine, indomethacin); the existence of a contraindication to the implementation any of the planned physical agents (pregnancy, fever, malignancy, acute infectious disease, decompensation of vital organs, the presence of metal in tissue, diseases or damage to the integrity of the skin at the electrode to application); or hypersensitivity to alpha-lipoic acid of 60 adult (18 years or older), galactose intolerance, glucose-galactose malabsorption or Lapp lactose deficiency.

The study was conducted during three diagnostic and therapeutic cycles, each of which lasted 16 days and the period of time between cycles was 6±1 week with a total study duration of six months.

The subjects were divided into two groups of 30 patients with diabetes mellitus type 2 and DSMP, based on clinical symptoms and signs, as well as the parameters of EMNG findings. Using a computer random number generator, each patient was randomly allocated to one of the two experimental groups (therapeutic arms): Group A or B.

Group A patients were treated with combined physical procedures. The method of combined physical procedures included stable galvanization (SG), pulsed electromagnetic field (PEMP), TENS, and exercise. SG (Galvan plus, Electronic Design Medical, Serbia) was applied once a day for 20 minutes, using the standard rectangular electrodes placed longitudinally along both legs. The intensity was 0.1–0.5 mA/cm^2, depending on the subjective feelings of patients. PEMP (Magomil-2, Electronic Design Medical, Serbia) was applied once a day for 30 minutes along both lower legs and feet, over the antenna at a frequency of 10 Hz and intensity of 40 mT. TENS (TENS-2, Electronic Design Medical, Serbia) was applied once a day for 30 minutes along both feet longitudinally, at a frequency of 85 Hz and with short-term pulses (4 ms) (appliance). Exercise performed once a day for 30 minutes, according to individually tailored protocol. Active and active-assisted exercises were used to the point of pain for strengthening the muscles of the lower extremities and to increase the range of motion of all

joints in the lower extremities.

The second group (Group B) patients were treated with alpha lipoic acid in accordance with the conditions specified in the license for marketing of the medicine in Serbia (indications, dosage regimen, precautions, etc.) and standard clinical practice. In the period from 2 to 15 days of hospitalization, patients were treated with intravenous administration of alpha lipoic acid (600 mg in 500 ml of 0.9% NaCl, once a day). Upon completion of hospitalization, and during the entire period of the study, subjects have continued to regularly take oral alpha lipoic acid at a dose of 600 mg (one tablet a day, in the morning before breakfast).

On patient admission and upon the completion of the last (third) diagnostic and therapeutic cycle (after 6 months) an analysis of EMNG of the sensory and motor nerves of the lower extremities was conducted (n. peroneus and n. suralis). EMNG testing was performed using the latest-generation Medtronic Keypoint (Denmark, Skovlunde, www.medtronic.com). The duration of the procedure was about 45 minutes, including reading of the results. The method examines individual nerve conduction velocity by registering evoked potentials directly from the sensitive fibers, while the motor fibers are tested through evoked potentials with or from muscles innervated by these neurons. The procedure does not require any preparation, and it is performed by placing surface (skin) and/or deep electrodes, usually both types of electrodes, as decided by the doctor who is performing the examination of n. peroneus and n. suralis.

The median value, standard deviation (SD), median, minimum and maximum values, as well as the normality of the distribution of all continuous variables were determined, using the Shapiro-Wilk test. In order to compare the mean values of continuous variables within the tested groups, the paired *t*-test was used for data sets with normal distribution, or alternatively Wilcoxon's test of matched pairs. Differences between the compared groups were investigated using the independent t-test or the Mann-Whitney test data sets without a normal distribution. The χ^2 test was used to compare the frequency (incidence) of categorical (dichotomous) variables. Statistical significance was accepted for all the results where the probability of the null hypothesis was less than 5% ($p<0.05$). The research results are presented in tabular form. All statistical calculations were carried out using the commercial software package SPSS version 20.0.

RESULTS

The basic characteristics of the patients in group A, the physical therapy group and group B, the alpha lipoic acid group are given in Table 1. Both groups were homogeneous by gender (p=0.598), diabetes mellitus genetic heritage (p≈1.000), active cigarette smoking (p=0.347), profession (p=0.837), age (p=0.09), body mass index (p=0.773), duration of DM (p=0.09) and laboratory test results: HbA1c (p=0.403), urea (p=0.679), and creatinine (p=0.524).

Table 2 shows the results of the electroneurographic test of n. peroneus. At the end of the intervention there were statistically significant improvements in terminal latency ($p<0.001$) and the amplitude of the action potency (p=0.032) in group A patients, while in group B patients showed statistically significant improvements in conduction velocity ($p<0.001$) and terminal latency (p=0.001) of n. peroneus. At the beginning of the study group A and group B showed no significant differences in the monitored electroneurographic parameters; they were homogeneous in speed of enforcement, p=0.385, terminal latency

Table 1 . Characteristics of the patients with DSMP

Characteristic		Group A (n = 30)	Group B (n = 30)	Significance
number (%)				
Gender	male	11 (36.7%)	13 (43.3%)	no
	female	19 (63.3%)	17 (56.7%)	
Hereditary DM	Yes	13 (43.3%)	13 (43.3%)	no
	No	17 (56.7%)	17 (56.7%)	
Active smoking	Yes	8 (26.7%)	5 (16.7%)	no
	No	22 (73.3%)	25 (83.3%)	
Profession (p/e/ue)		76.7/20/3.3	73.3/20/6.7	no
mean ± SD				
Age (years)		63.2±7.7	62.8±8.3	no
Body Mass Index (kg/m^2)		27.2±4.6	27.2±3.9	no
Duration of diabetes (yr)		12.2±7.6	11.7±5.7	no
HbA1c (%)		7.8±1.9	7.3±1.2	no
Urea (mmol/l)		6.5±2.9	6±2.1	no
Creatinine (μmol/l)		81.1±22.2	76.3±17.7	no
Motor conduction velocity of n. peroneus		40.6±3.8	39.5±5.1	no
Sensory conduction velocity of n. suralis		31.8±21	31.6±24.1	no

p: retired; e: employed; ue: unemployed

p=0.849 and amplitude of action potential p=0.525. At the end of the intervention there were again no significant differences in the speed of implementation (p=0.845), terminal latency (p=0.563), or the amplitude of the action potency (p= 0.881).

Table 3 shows the results of the electroneurographic examination of n. suralis. At the end of the intervention in group A patients showed statistically significant improvements in conduction velocity (p<0.001) and terminal latency (p=0.014), while group B patients also showed statistically significant improvement in conduction velocity (p=0.007) and terminal latency (p = 0.008), too. At the beginning of the study group A and group B showed no significant differences in the monitored ENG parameters; they were homogeneous in enforcement speed, p=0.658, terminal latency p=0.576 and amplitude of action potential p=0.489. At the end of the intervention, there were again no significant differences in speed of implementation (p=0.794), terminal latency (p=0.737), or the amplitude of the action potency (p=0.372).

DISCUSSION

The results of our study show that both treatment modalities, alpha-lipoic acid and the program of physical therapy, improved the electromyoneurography parameters of the patients with diabetic neuropathy, with approximately comparable extent. A larger number of studies have examined the effects of the physical therapy and alpha lipoic acid in patients with neuropathy. However, the variety of physical methods, treatment protocols, patient characteristics and etiological factors of neuropathy results in a distinct methodological heterogeneity, which is why the results can only be indirectly compared to each other, and to the results of our study, as well.

A clinical study[15] showed the effect of pulsed electromagnetic fields on the regeneration of nerves in patients with DSMP, but without a statistically significant reduction of pain (VAS). In the study by Bosy et al.[16], an increase in the speed of conduction was found through n. peroneus after application of magnetic therapy to n. suralis. Our results are consistent with that study, except that in our study, in addition to a magnetic therapy, electrotherapy (TENS and SG) was applied, too.

In the study by Graack et al.[17], after application of electromagnetotherapy, a statistically significant reduction the distal latency of n. peroneus and a significant increase in the speed of conduction through n.peroneus were shown, but there was no significant change in the amplitude of the action potential of n. peroneus. Our results also indicated there was a statistically significant increase in the speed of conduction through n.peroneus in group B patients, and a reduction in the distal latency of n.peroneus in both groups of A and B; however, no statistically significant difference was found between the two therapeutic

Table 2 . Nerve conduction study results for n.peroneus

Parameter		Group A (n = 30)	Group B (n = 30)	Significance
Motor conduction velocity of n.peroneus (m/s)	before	40.6 ± 3.8	39.5 ± 5.1	no
	after	41.6 ± 4.4	41.1 ± 5	no
	Significance	no	***	
Distal latency of n.peroneus (ms)	before	4 ± 1	4.2 ± 1.5	no
	after	3.5 ± 1	3.8 ± 1.4	no
	Significance	***	***	
Action potential amplitude of n.peroneus (mV)	before	3.8 ± 2.2	3.3 ± 2.2	no
	after	4.4 ± 2.6	3.6 ± 2.1	no
	Significance	*	no	

Group A: physical therapy; Group B: alpha lipoic acid; * < 0.05 ** < 0.01 *** < 0.001

Table 3 . Nerve conduction study results for n.suralis

Parameter		Group A (n = 30)	Group B (n = 30)	Significance
Sensory conduction velocity of n.suralis (m/s)	before	31.8 ± 21	31.6 ± 24	no
	after	40.1 ± 25.6	32.2 ± 27.7	no
	Significance	***	**	
Distal latency of n.suralis (ms)	before	2.6 ± 2.8	2.1 ± 1.7	no
	after	1.9 ± 1.4	1.8 ± 1.5	no
	Significance	*	**	
Action potential amplitude of n.suralis (mV)	before	2.9 ± 2.3	2.7 ± 2.7	no
	after	3 ± 2.7	2.7 ± 2.8	no
	Significance	no	no	

Group A: physical therapy; Group B: alpha lipoic acid; * < 0.05 ** < 0.01 *** < 0.001

modalities. Unlike the study by Graack et al., the therapy applied in our study increased the amplitude of the action potential of n. peroneus in group A patients.

A four-year study[18] reported that the performance of exercise resulted in a statistically significant increase in the speed of conduction through n. peroneus, while the conduction velocity through n. suralis did not significantly change. Several other studies have confirmed these results[19–22]. In our present study, the performance of exercise combined with magnetotherapy and electrotherapy also achieved a significant increase in the speed of conduction through n.peroneus in group B patients, but the application of these physical agents also significantly increased the speed of conduction through n. suralis.

A study by Fisher et al.[23] demonstrated statistically significant improvements in EMNG parameters (speed of conduction, amplitude and latency through the motor and sensory nerves) after a 24-week exercise program for patients with DSMP. Our results are in agreement with the results of that study, but out method differed in that it combined training with electrotherapy and magnetotherapy. There was also a difference in the duration of treatment: physical therapy was shorter in our study than in the study by Fischer et al.

A study[24] showed that the use of alpha lipoic acid in the treatment of DSMP led to a significant increase in the speed of conduction through n. peroneus and n. suralis which partially matches the results of our present study. These results suggest beneficial effect of combining these two methods of treatment for patients with DSMP, which should be studied in future research.

The application of physical agents and alpha lipoic acid mentioned above favorably influenced the course and outcome of patients with symmetrical distal sensorimotor diabetic polyneuropathy. This was reflected in a significant improvement in electrophysiological parameters (conduction velocity, amplitude and latency) of the motor and sensory nerves (n. peroneus, n. suralis). These results present further evidence in favour of the use of physical agents in the treatment of diabetic sensorimotor polyneuropathy. They also contribute to the theoretical basis for the planning of further investigations of other important aspects of different therapeutic strategies, such as the efficacy and safety of combined treatments and economic studies.

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Understanding the Serum Vitamin B_{12} Level and its Implications for Treating Neuropsychiatric Conditions: An Orthomolecular Perspective

Author: Jonathan E. Prousky, ND, MSc[1,2]

[1] Chief Naturopathic Medical Officer, Professor, Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario, M2K 1E2, Tel: 416-498-1255 ext. 235, email: jprousky@ccnm.edu
[2] Editor, Journal of Orthomolecular Medicine, email: editor@orthomed.org

Abstract: *Vitamin B_{12} (cobalamin) ranks among the most useful, safe and effective orthomolecules when treating a diverse array of neuropsychiatric conditions. However, most clinicians do not consider vitamin B_{12} important unless the serum level is below laboratory reference ranges. Ten research reports, summarized here, indicate metabolic consequences from low-normal (but not deficient) serum B_{12} levels, and/or clinical improvements following therapy that markedly increased serum B_{12} levels. My clinical experience, along with the summarized reports, suggests that (1) serum levels of vitamin B_{12} not "classically" deficient by current laboratory standards are associated with neuropsychiatric signs and symptoms, and (2) clinical improvement results when serum vitamin B_{12} levels are optimized or markedly increased following vitamin B_{12} treatment. Vitamin B_{12}'s mechanisms of action are believed to include increased S- adenosylmethionine production, improved methylation, decreased plasma and brain homocysteine, compensation for inborn errors of metabolism, normalized gene expression, correction of long-latency vitamin B_{12} debt, and anti-inflammatory activity. Clinicians may wish to re-evaluate the importance of lower-than-optimal serum vitamin B_{12} levels, pursue additional testing such as urinary methylmalonic acid, and consider the potential benefits of vitamin B_{12} treatment.*

Introduction

For approximately twelve years I have been using pharmacological doses of nutrients to mitigate a variety of neuropsychiatric signs and symptoms, such as anxiety, aphasias (i.e., both expressive and receptive types), ataxia, cognitive impairment, depressions, delusions, developmental delays, fatigue, hallucinations, insomnia, irritability, memory problems, mood swings, muscle weakness, neuralgias, neuropathy, obsessions, paranoid ideations, paresthesias, psychoses, and/or seizures. When treating such a diverse array of neuropsychiatric presentations, vitamin B_{12} (cobalamin) ranks among the most useful, versatile, safe, and effective orthomolecules at my disposal. Despite my success in observing improvements among my patients prescribed vitamin B_{12}, recognition of vitamin B_{12} insufficiency remains neglected. Most clinicians do not consider vitamin B_{12} important unless the serum level is deficient when indicated by laboratory reference ranges. Vitamin B_{12} therapy con-

tinues to be viewed by many mainstream-minded clinicians as unexpected or unwarranted. The purpose of this paper is therefore to show the rationality of using vitamin B_{12} therapeutically, even in the absence of "classical" deficiency.

What Serum Vitamin B_{12} Level Defines "Classical" Deficiency?

A number of publications discuss the serum levels of vitamin B_{12} that reflect "classical" deficiency. According to one author, a patient is considered to be deficient in vitamin B_{12} when the serum vitamin B_{12} level is < 100 pg/mL (74 pmol/L).[1] In another article, deficiency was defined as having a serum vitamin B_{12} level < 203 pg/mL (150 pmol/L) on two separate occasions, or when the serum vitamin B_{12} level is < 203 pg/mL (150 pmol/L) and total serum homocysteine level is > 13 μmol/L or serum methylmalonic acid > 0.4 μmol/L.[2] In the province where I reside, most laboratories consider a patient to be deficient in vitamin B_{12} if the serum level is less than 149 pg/mL (110 pmol/L). When vitamin B_{12} reaches a level that would reflect "classical" deficiency, it is important to determine and rule-out underlying causes (e.g., alcoholism, pernicious anemia, and vegetarian diet) and prescribe appropriate vitamin B_{12} replacement therapy.

Review of Ten Neuropsychiatric Research Reports about Vitamin B_{12}

While vitamin B_{12} deficiency has been associated with problems in cognition, mood and psychosis, and less commonly, anxiety, three patients with serum vitamin B_{12} levels outside of the "classical" deficient range also suffer from various neuropsychiatric signs and symptoms reflective of vitamin B_{12} "insufficiency." When these patients are given therapeutic doses of vitamin B_{12}, their serum levels further increase and their clinical picture usually improves. I summarized 10 research reports that suggest metabolic consequences from lower-normal (but not deficient) serum vitamin B_{12} levels, and/or noted clinical improvements following marked increases in serum vitamin B_{12} levels.

Report #1: 29 Subjects with Fatigue

Twenty-nine subjects (7 male and 22 female; mean age 41.5 years) complaining of idiopathic fatigue or tiredness completed a double-blind cross-over trial.[4] The subjects were provided with intramuscular (IM) injections of hydroxocobalamin (5 mg twice weekly for two weeks) or identical-looking placebo injections, followed by a rest period of two weeks, and then a similar course of hydroxocobalamin or identical-looking placebo injections depending on treatments given during the initial two week trial period. Symptoms were evaluated by a daily self-rating card that assessed appetite, general feeling of well-being, fatigue, mood (i.e., level of happiness), injection response (i.e., how the injection made the subject feel), and sleep. Those subjects who received the placebo in the first two week period showed a favourable response to hydroxocobalamin in the second period on all measurements made. The results showed statistical significance with respect to general well-being ($p=0.006$) and happiness ($p=0.032$). The initial mean serum vitamin B_{12} level was 358.4 pg/mL (264.4 pmol/L). By the end of treatment serum concentrations had risen to more than 2000 pg/mL (1476 pmol/L) in all but three of the total 29 subjects. The three subjects that did not have serum vitamin B_{12} values above 2000 pg/mL, had concentrations at or above 450 pg/mL (332 pmol/L).

The authors of this study concluded that vitamin B_{12} has a "tonic" effect. They reasoned that the response to vitamin B_{12} was related to pharmacological factors such as the ability of the vitamin to penetrate into the brain or neurons, or to an influence of vitamin B_{12} on neural metabolism. While none of the patients had serum levels of vitamin B_{12} that would be considered deficient, they did respond favourably to vitamin B_{12} administration after their serum levels were dramatically increased by intramuscular injections.

Report #2: 61 Patients - Serum vs. Brain Status of Vitamin B_{12}

This study sought to determine to what extent vitamin B_{12} in the serum is a real reflection of vitamin B_{12} status of brain tis-

sue.[5] It was comprised of three groups of patients and one control group. Group 1 involved 23 patients aged 60-85 with dementia, group 2 involved 16 patients aged 30-60 with organic affective syndrome, group 3 involved 10 female patients aged 25-40 with postnatal depression (and complaints of neurasthenia), and the control group of 12 patients aged 25-50. All patients were normal haematologically, had normal liver function and kidney function tests, but did have evidence of "soft" neurologic symptoms (i.e., some combination of encephalopathy and/or polyneuropathy or neuropathy). When the serum levels of vitamin B_{12} were tested, normal values (200-800 pg/mL; 148-590 pmol/L) were found in 45 of the 49 patients from groups 1-3. All 12 patients in the control group had serum B_{12} levels in the normal range. Deficient cerebrospinal fluid levels (CSF) of vitamin B_{12} (<5 pg/mL; <3.7 pmol/L) were found in 30 of the total 49 patients (or in 26 of the 45 patients with normal serum levels). All 12 patients in the control group had CSF levels in the normal range (>10 pg/mL; >7.4 pmol/L). Because there was a marked difference between both compartments when measured, these results indicate that a potentially treatable vitamin B_{12} deficiency will be overlooked in a significant portion of patients if CSF B_{12} levels are not included in the assessment. Ten patients were given six weeks of twice weekly IM treatment of hydroxocobalamin (1,000 mcg) plus daily treatment with an oral supplement containing 50 mg zinc-DL-aspartate and 250 mg of taurine. Two patients were given 6 weeks of a daily supplement containing cyanocobalamin (0.1 mg) plus 50 mg zinc-DL-aspartate and 250 mg of taurine. **Table 1** (below) highlights the changes in both serum and CSF that resulted from vitamin B_{12} treatment. Treatment with IM hydroxocobalamin produced more significant increases than oral cyanocobalamin in the patients' CSF levels of vitamin B_{12}.

In group 1 (patients with dementia), the authors speculate that zinc deficiency and its corresponding high levels of copper block the transport of B_{12} in the choroid plexus (and therefore, the CSF), similar to the effects of free radical chain reaction inducers like mercury, cadmium and other neurotoxins. Group 2 (patients with organic affective syndrome), all had exposures to toxic chemicals (i.e., alcohol, industrial solvents or halogenated hydrocarbons), which were considered causative in their neurasthenic-depressive clinical presentation. The authors speculate that these neurotoxins may block the entry of vitamin B_{12} into the brain, leading to CSF deficiency of the vitamin. In group 3 (patients with postnatal depression), the authors suggest that estrogens or estrogen-receptor binding chemicals (e.g., halogenated hydrocarbons) have an effect on B_{12} transport through the blood-brain barrier and choroid plexus, thus causing deficiency of the vitamin with the CSF.

Table 1. Changes in serum and CSF vitamin B_{12} concentrations following treatment

Group	Pre-treatment serum B_{12} (pg/ml)	Pre-treatment CSF B_{12} (pg/ml) serum	Post-treatment serum B_{12} (pg/ml)	Post-treatment CSF B_{12} (pg/ml)
IM injection (n=10)	310 (229 pmol/L) (average)	<5 (<3.7 pmol/L) (average)	>2400 (>1771 pmol/L) (average)	70 (52 pmol/L) (average)
Oral (Patient #1)	430 (317 pmol/L)	14 (10 pmol/L)	2400 (1771 pmol/L)	21 (15.5 pmol/L)
Oral (Patient #2)	450 (332 pmol/L)	<5 (<3.7 pmol/L)	>2400 (>1771 pmol/L)	9.6 (7.1 pmol/L)

Report #3: 16 Patients with Dementia and 13 Patients with Neurasthenia

In another publication by the authors of report #2, 16 geriatric patients aged 60-85 years with dementia or organic affective syndrome with co-existing dementia were assessed.[6] All patients had normal liver function and no gross haematological abnormalities. These patients did have signs and symptoms of polyneuropathy. Three patients had low levels of serum B_{12}, and low levels of CSF B_{12}. The remaining 13 patients had normal serum B_{12} levels (220-540 pg/mL; 162-398 pmol/L), with nine of them also having deficient CSF B_{12} levels. Five patients that had normal serum levels and deficient CSF levels were given three months of treatment with parenteral hydroxocobalamin (unstated dose). After three months, they experienced clinical improvement and had a marked rise in their CSF B_{12} levels (50-90 pg/mL; 37-66 pmol/L).

In a second group of 13 patients (29-50 years of age) with neurasthenic symptoms, the vitamin B_{12} levels were assessed in both the serum and CSF. All patients had normal liver function and no gross haematological abnormalities. These patients did have 'soft' neurological signs of encephalopathy and neuropathy. All 13 patients had normal serum levels of vitamin B_{12} (range, 280-750 pg/mL; 207-553 pmol/L), but 11 of them had deficient CSF levels (<5 pg/mL; <3.7 pmol/L). By not performing routine CSF analysis, the majority of these patients would not have been found to have a vitamin B_{12} deficiency.

The authors concluded that all patients displaying organic mental symptoms should have their CSF levels of vitamin B_{12} assessed. I am of the opinion that routine CSF measurements of vitamin B_{12} are impractical, expensive, and invasive. Perhaps another way of interpreting these results is to know that serum vitamin B_{12} levels within normal ranges might not reflect what is happening within the brain. To encourage normal or even optimal CSF levels of vitamin B_{12}, marked increases in serum levels of the vitamin might be achieved through IM administration.

Report #4: 14 Patients with Dementia, Degenerative Types

Vitamin B_{12} levels in the serum and the CSF were assessed in 14 patients with dementia.[7] Eleven of these patients had degenerative types of dementia, such as Alzheimer's disease, senile dementia, and Pick's disease. The serum vitamin B_{12} levels in all patients were normal (500-1,300 pg/mL; 369-959 pmol/L). CSF levels of vitamin B_{12} did not correlate with severity of the dementia. After oral methylcobalamin (2,000 mcg per day), neither serum or CSF levels of vitamin B_{12} were significantly elevated. On the other hand, when the patients were given the same oral dose plus daily IM injections of methylcobalamin (500 mcg), marked elevations occurred in both the serum and CSF compartments. This study is compelling on two fronts. First, the serum vitamin B_{12} ranges used in this study are much higher than those reported in other publications.[1-5] Perhaps in Japan they are aware that a higher serum vitamin B_{12} level correlates with better health; thus, the need for a reference range that "captures" more deficient patients. Second, IM methylcobalamin was the only way to markedly increase both serum and CSF levels of vitamin B_{12} among the patients with dementia. Oral methylcobalamin did not appreciably increase serum and CSF levels of vitamin B_{12}.

Report #5: 8 Patients with Personality Symptoms

Eight patients were administered IM hydroxocobalamin to treat their personality symptoms, as assessed by the Minnesota Multiphasic Personality Inventory (MMPI).[8] The patients in this trial had the following diagnoses: paranoid schizophrenia (one patient), angioneurotic edema (one patient), cancer prevention (one patient), depression (two patients), recurrent duodenal ulcer (one patient), insomnia (one patient), and cocaine addiction (one patient). All of the patients were 16 years of age and older and not on any medication. They were taking a variety of supplements such as vitamins, minerals, and unsaturated fats. Their serum

vitamin B_{12} levels were within the laboratory's normal range (115-800 pg/mL; 85-590 pmol/L). All patients, through trial and error, were given injections of hydroxocobalamin to establish ideal doses of the vitamin (doses ranged from 3,000 mcg four times each week to 9,000 mcg per day). Serum vitamin B_{12} levels were drawn when patients felt the greatest sense of well-being and were also drawn after the injections were discontinued for 5-7 days. Patients also completed the MMPI numerous times during the trial period. The highest serum vitamin B_{12} levels (average: 465,173 pg/mL; 343,205 pmol/L) were associated with MMPI patterns at or closer to normal (profile elevation average: 56.1). With lower serum vitamin B_{12} levels (average: 110,611 pg/mL; 81,609 pmol/L), the MMPI patterns showed much more emotional distress (profile elevation average: 67.5).

The author concluded that vitamin B_{12} dependency disorders are common and neglected by the medical profession because: (1) the body level of vitamin B_{12} needed for full biological efficiency is unknown; (2) patients might have a deficiency in transporting vitamin B_{12} into their tissues (low levels of transcobalamin II); and (3) a large increase in a vitamin level might be needed to "force" one or more abnormal chemical reactions to proceed normally.

Report #6: Two patients with Sleep-wake Disorders

Two adolescent patients with persistent sleep-wake schedule disorders responded to treatment with oral methylcobalamin.[9] A 17-year-old male had hypernychthemeral syndrome (non-24-hour circadian rhythm disorder) and was unable to attend school despite trying various medications. A 15-year-old girl had delayed sleep phase syndrome (DSPS) and was similarly unable to attend school despite numerous medication trials. Both patients did not have any laboratory or clinical evidence of vitamin B_{12} deficiency or hypothyroidism. Improvement of their sleep-wake schedule disorders appeared immediately after the administration of high doses (3,000 micrograms per day) of oral methylcobalamin. Serum concentrations of vitamin B_{12} during the treatment period were in the high range of normal or above normal. The female patient's serum level of B_{12} was 1,078 pg/mL (795 pmol/L) after two weeks of treatment. Her baseline serum B_{12} level was not provided in the report. The male patient's baseline serum vitamin B_{12} level was 589.5 pg/mL (434.9 pmol/L) and was measured three more times during treatment. His last serum vitamin B_{12} measurement during treatment was 1,161.6 pg/mL (857.03 pmol/L). For the male patient, treatment reduced the sleep-wake cycle from 24.6 hours to 24.0 hours, which was significant since his sleep-wake rhythm became entrained to the environmental 24-hour rhythm. For the female patient with DSPS, treatment decreased sleep from 10 hours to seven hours, and the time of sleep onset normalized from 2 a.m. to midnight.

It appears that these patients responded when their serum levels increased to the high range of normal, or to levels exceeding normal. It was concluded that vitamin B_{12} benefited these patients either by enhancing the phase-setting effects of light through some action on the eye or retinohypothalamic tract, or by a direct phase-setting effect.

Report #7: Patient with Hypersomnia

This communication describes the successful use of oral methylcobalamin in a 32 year-old-male patient with recurrent hypersomnia of 12 years duration.[10] He would have episodes lasting a few times each year, but when the episodes increased to once every month, he was referred to a psychiatrist for further evaluation and treatment. He was prescribed 1500 mcg of oral methylcobalamin from May 1993 until October 1993. Episodes of hypersomnia stopped during this treatment period and did not recur during the 17 months of follow-up. The baseline serum B_{12} level was 420 pg/mL (310 pmol/L), and increased to 980 pg/mL (723 pmol/L) one month after B_{12} administration.

This patient's response to vitamin B_{12} therapy suggests that it was effective at preventing his recurrent hypersomnia, although a spontaneous remission was possible. Vitamin B_{12} was pre-

sumed to increase sensitivity to environmental conditions including light stimulation, thereby increasing the patient's level of consciousness and preventing episodes of hypersomnia.

Report #8: Patients with Depression

This study determined if there was an association between vitamin B_{12} and folate levels and the six-month treatment outcome in patients with major depressive disorder.[11] Haematological indices, erythrocyte folate and serum vitamin B_{12} levels were determined in 115 outpatients with major depressive disorder at baseline and again six months later. The 17-item Hamilton Depression Rating Scale (HDRS) was also assessed at baseline and again six months later. None of the patients in this study had deficient vitamin B_{12} levels. In the non-response group (n=40), the average baseline vitamin B_{12} measurement was 470.5 pg/mL (347.2 pmol/L). In the partial response group (n=34), the average baseline vitamin B_{12} measurement was 536.6 pg/mL (396.0 pmol/L). The full response group (n=41) had an average baseline vitamin B_{12} measurement of 594.9 pg/mL (439.1 pmol/L). Higher baseline vitamin B_{12} levels were associated with a better outcome. There was no relationship between the haematological indices and the six month outcome. A positive correlation was found between both the vitamin B_{12} level at baseline ($r = 0.39$, $p < 0.001$) and on follow-up ($r = 0.26$, $p = 0.006$), and the decline (i.e., improvement) in the HDRS score during six months of treatment.

The authors concluded that the serum level of vitamin B_{12} may correlate with recovery from major depression. They speculated that patients might need more vitamin B_{12} because of lower intakes of vitamins from food or impaired assimilation from the gastrointestinal tract, higher metabolic rates, issues in monoamine synthesis, and/or the elevations of homocysteine leading to excitotoxic reactions within the brain.

Report #9: Survey of 1,000 patients for B_{12} levels

This study involved a total of 1,000 individuals, aged 75 years or older living in their homes and registered with three general practitioners in Banbury, Oxfordshire, England.[12] Deficient serum vitamin B_{12} concentrations were identified in approximately 13% (125) of study subjects and were associated with memory impairment and depression. These subjects had serum vitamin B_{12} levels <180 pg/mL (133 pmol/L). After adjusting for various parameters (age, sex and smoking), subjects with serum vitamin B_{12} or holotranscobalamin (holoTC) in the bottom compared with top quartiles had a 2-fold risk (OR = 2.17; 95% CI 1.11-4.27) and a 3-fold risk (OR = 3.02; 95% CI 1.31-6.98) of cognitive impairment, respectively. The mean vitamin B_{12} levels in the bottom two quartiles were 169.4 pg/mL (125 pmol/L) and 251 pg/mL (185 pmol/L) respectively. Absence of ankle tendon jerks was also associated with low vitamin B_{12} status.

Treatment with vitamin B_{12} (1,000 mcg hydroxocobalamin IM) once each month for 3 consecutive months corrected the biochemical abnormalities, but had no effect on any of the clinical measurements. In older individuals without anaemia, low vitamin B_{12} concentrations were associated with cognitive impairment and missing ankle tendon jerks.

Report #10: 107 Patients without Cognitive Impairment

This study involved 107 community-dwelling subjects aged 61-87 years without cognitive impairment at enrollment.[13] It was a prospective study that assessed the relationship between markers of vitamin B_{12} status and brain volume loss over a 5-year period. All subjects were assessed annually by clinical examination, magnetic resonance imaging scans, and cognitive tests. Blood was drawn at baseline for measurement of serum vitamin B_{12}, transcobalamin (TC), holotranscobalamin (holoTC), methylmalonic acid (MMA), total homocysteine (tHcy), and serum folate. Brain volume loss was greater among those with lower serum vitamin B_{12} and holoTC levels and higher plasma tHcy and MMA levels at baseline. Linear regression analysis showed that associations with vitamin B_{12} and holoTC remained significant after adjustment for various parameters

(i.e., age, sex, creatinine, education, initial brain volume, cognitive test scores, systolic blood pressure, ApoE epsilon4 status, tHcy, and folate). Increased rate of brain volume loss (odds ratio 6.17, 95% CI 1.25-30.47) was associated with vitamin B_{12} in the bottom tertile (< 417.3 pg/mL; <308 pmol/L).

The authors concluded that low vitamin B_{12} status should be investigated as a treatable cause of brain atrophy and of apparent subsequent cognitive impairment in the elderly.

Purported Mechanisms of Action for Vitamin B_{12}

My clinical experience and the above-noted reports suggest the following: first, serum levels of vitamin B_{12} that are not "classically" deficient by current laboratory standards are associated with neuropsychiatric signs and symptoms not limited to declines in cognitive functioning (i.e., neurological deficits), tiredness, affective disorders, psychosis, insomnia/sleep-wake disturbances, and even brain volume loss; and second, a variety of neuropsychiatric signs and symptoms improve when serum vitamin B_{12} levels are optimized or markedly increased following vitamin B_{12} treatment.

Vitamin B_{12} participates in the production of S-adenosylmethionine (SAM), a donator of methyl groups, and therefore it plays a decisive role in the functioning of the neuropsychiatric system. An adequate production of SAM facilitates the formation of phospholipids that comprise neuronal myelin sheaths and cell receptors,[14] and the synthesis of monoamine neurotransmitters.[14,15] Insufficient vitamin B_{12} would decrease the production of SAM, which would impair methylation and, consequently, impair the metabolism of neurotransmitters, phospholipids, myelin and receptors.

Therapeutic vitamin B_{12} supplementation might also lower plasma and brain levels of homocysteine, which might mitigate, reverse, and potentially normalize damaged brain neurons. Elevations of homocysteine can cause neuronal injury by augmenting neuronal calcium influx, contributing to oxidative stress,[16] activating N-methyl-D-aspartic acid channels that stimulate glutamate excitotoxicity,[17] lowering cerebral concentrations of N-acetyl-aspartate,[18] and inducing cerebral mitochondrial dysfunction.[19]

Four interrelated mechanisms for vitamin B_{12}'s therapeutic benefits were highlighted by Kaplan et al[20] when delineating the potential reasons by which vitamins and minerals influence mood. Supplemental vitamin B_{12} might correct for inborn errors of metabolism. Pauling,[21] Newbold,[8] and Ames[22] reasoned that micronutrients, which would include vitamin B_{12}, are required to increase coenzyme concentrations and therefore correct defective enzymatic activity by enabling abnormal chemical reactions to proceed normally. Another mechanism involves the correction of deficient methylation. Methylation deficiency has been described in the literature to be responsive to IM injections of vitamin B_{12} (as cyanocobalamin) in a patient with schizophrenia,[23] and has been identified as being part of the pathogenesis of schizophrenia.[24] A further mechanism involves the correction of altered gene expression. It is well established that nutrients influence genetic expression. Genotyping identified transcobalamin II (TCNII) gene variants among community-dwelling older women.[25] These gene variants lead to decreased vitamin B_{12} availability (i.e., tissue vitamin B_{12} deficiency), leading to reduced energy metabolism, and contribute to frailty pathology. It is possible that TCNII gene variants exist among individuals presenting with various neuropsychiatric signs and symptoms. Vitamin B_{12} supplementation might modify the TCNII genes (and possibly other vitamin B_{12} dependent genes) that depend on sufficient vitamin B_{12} levels and therefore modify the phenotypic expression of the implicated genes.

An additional mechanism reasons that micronutrients might resolve long-latency deficiency diseases. It has been argued that many chronic diseases (e.g., cancer, cardiovascular disease, and central nervous system degeneration) are long-latency effects.[26] Kaplan et al[20] cite the development of depression and bone density loss as an example of a long-latency

disease since it occurs many years following inadequate calcium absorption. With respect to vitamin B_{12}, perhaps some patients who present with neuropsychiatric signs and symptoms do so after years of vitamin B_{12} debt. This might explain why a disproportionate amount of patients with clinical features of vitamin B_{12} debt tend to be older as opposed to younger. However, I have seen young patients with clinical features of vitamin B_{12} debt as well. This mechanism is questionable since early childhood neuropsychiatric symptoms can result from suboptimal vitamin B_{12} status (e.g., due to dietary factors, gastrointestinal factors, and/or some other reasons), and would therefore be a short- and not long-latency effect.

One more mechanism that might account for some of vitamin B_{12}'s benefits has to do with its purported anti-inflammatory effects. It is known that vitamin B_{12} debt might lead to neurologic damage since deficiency in rats has been associated with increased tumour necrosis-alpha (TNF-alpha) and decreased epidermal growth factor (EGF), an important neurotrophic agent.[27] Supplemental vitamin B_{12} (in the form of methylcobalamin) has been shown *in vitro* to blunt inflammatory cytokine production in patients with rheumatoid arthritis.[28] While preliminary, vitamin B_{12} might reduce inflammation by modifying the levels of TNF-alpha and EGF within the body and perhaps within the brain as well.

Table 2 (p.85) highlights the biochemical reasons (underlying mechanisms) for vitamin B_{12}'s therapeutic effectiveness.

Evaluating Patients with Neuropsychiatric Signs and Symptoms

In addition to hypothesis-driven physical examination, all patients presenting with neuropsychiatric signs and symptoms should have their fasting serum vitamin B_{12} levels tested. I created/adapted an evaluation scheme by drawing from my clinical experience and combining a published guideline[1] with vitamin B_{12} laboratory reference ranges from several medical laboratories in Ontario. **Table 3**, (p.85) presents a diagnostic process to consider when reviewing serum vitamin B_{12} levels.

With respect to Table 3, urinary methylmalonic acid (uMMA) testing can identify tissue vitamin B_{12} deficiency when serum levels are considered normal by conventional laboratory standards.[29-31] While I have not found a large percentage of patients to have elevated uMMA levels (reflecting tissue vitamin B_{12} deficiency), I routinely requisitioned this test to investigate this possibility.

Treatment Options

Prior research does support a clinical trial of vitamin B_{12} in patients with neuropsychiatric signs and symptoms.[32] Hydroxocobalamin and methylcobalamin are the forms of vitamin B_{12} that I administer for therapeutic purposes. I tend to rely exclusively on methylcobalamin when a patient presents with neurologic abnormalities, and use a combination of methyl and hydroxo forms when neurologic and psychiatric abnormalities are present. There is evidence supporting the use of methylcobalamin for a variety of neurological diseases, such as Alzheimer's disease,[33,34] Bell's palsy,[35] and multiple sclerosis.[36] While there is proof that an oral dose of cyanocobalamin (1,000 mcg daily for 3 years) can effectively treat patients with pernicious anemia,[37] my clinical experience has shown it to be inferior to the other forms of vitamin B_{12}. A report did demonstrate a greater rise in the baseline serum vitamin B_{12} level following parenteral hydroxocobalamin (106% increase) compared to parenteral cyanocobalamin administration (78% increase).[38] Parenteral forms of vitamin B_{12} outperformed oral (43% increase) and sublingual (34% increase) cyanocobalamin in the same study. Methylcobalamin is believed to be effective whether it is administered parenterally or orally because positive clinical results have been reported irrespective of the method of administration.[35]

I have not observed any side effects or toxicity from methylcobalamin. The only rare side effect from hydroxocobalamin is an acneiform exanthema, particularly in women.[39] The lesions consist of loosely disseminated small papules or papulopustules on the face, the upper parts of the back and chest, and can spread to the upper arm. They go away

within a week after discontinuing regular injections and/or oral supplementation.

Although IM injections are clinically more efficacious than oral forms of vitamin B_{12}, the frequency, dose, and method of administration must be individualized to each patient. Some patients respond clinically to 1,000 mcg IM of either form each month, while other patients require 5,000 mcg twice each week of IM methylcobalamin to control their symptoms. A trial-and-error approach based on patient response, willingness to comply with regular IM injections, and/or the capacity to self-administer injections is needed when using vitamin B_{12} therapeutically.

Here, I present two cases from my clinical practice showing the benefits of maintaining high serum levels of vitamin B_{12}. Written consent was obtained from these patients for publication of this report.

Case #1

A 47-year-old male presented to my private practice several years ago. He first started having anxiety symptoms 20 years ago coupled with obsessive compulsive behaviours. He would often drive to and from locations worrying about hitting someone,

Table 2. Purported mechanisms of action for vitamin B_{12}

1. Increases S-adenosylmethionine, which participates in the formation of phospholipids that comprise neuronal myelin sheaths and cell receptors, and the formation of monoamine neurotransmitters
2. Lowers plasma and brain levels of homocysteine, which might mitigate, reverse, and potentially normalize damaged brain neurons
3. Corrects inborn errors of metabolism
4. Corrects deficient methylation processes
5. Corrects altered gene expression
6. Resolves long-latency vitamin B_{12} debt (?)
7. Anti-inflammatory properties

Table 3. Evaluating serum vitamin B_{12} results in patients with neuropsychiatric signs and symptoms

Serum Vitamin B_{12} Result	Further Testing	Intervention
< 149 pg/ml (110 pmol/L)	Search for underlying causes which might include anti-parietal, anti-intrinsic factor antibody testing, gastroscopy, and rule-out malabsorption	Treat with vitamin B_{12}
149-400 pg/ml (110-295 pmol/L)	Urinary methylmalonic acid to identify tissue vitamin B_{12} deficiency	Empiric trial with vitamin B_{12}
> 400 pg/ml (> 295 pmol/L)	Not required	Empiric trial with vitamin B_{12}

or that he had in fact hit someone with his car. He would also worry excessively about having cancer and other diseases. His symptoms became so bad that at 34 years of age he had a nervous breakdown. The patient was on zoloft® (sertraline hydrochloride) at a dose of 75 mg daily and had used antidepressants for 13 years. The Zoloft®, according to his report, improved his symptoms by about 80%. He had an initial Beck Anxiety Inventory (BAI) score of 28, placing him in the "severe anxiety" category. All laboratory tests were normal (red blood cell magnesium and folate, ferritin, fasting plasma glucose, and complete blood count). His serum vitamin B_{12} result was above normal at 343 pg/mL (253 pmol/L), but not optimal by my standards.

On December 11th, he was given an intramuscular injection of 5,000 mcg of vitamin B_{12} (methylcobalamin). He was also prescribed 5 mg of oral methylcobalamin to take daily. On January 22nd, he had his second follow-up appointment. He could not believe the improvement. He was able to reduce the Zoloft® to 50 mg, and noted that his anxiety seemed to be well controlled. His BAI score decreased to 11 (mild anxiety). The patient's plan was to wean off the zoloft® over the next few months.

On March 28th, another serum vitamin B_{12} was test was done. His level increased to greater than 1,762 pg/mL (1,300 pmol/L). He returned for another follow-up on September 17th and reported having had a stressful summer. Even though he had plenty of worries (selling his home, moving to a new home, and trying to have a baby), he was able to wean himself off his medication during the month of May. This was the first time in 13 years that he was able to discontinue mainstream antidepressant medication and feel relatively normal and symptom free.

Case #2

This 49-year-old female patient presented to my clinical practice. She described herself as being "Type A" while working in a high-pressure advertising position for the past 23 years. Two years prior to my consultation, she had an episode where words became blurry on her computer screen, she could not grab things with her hands, and she could not speak. She recalled that during the episode, stop signs appeared backwards and she could not even remember her dog's name. A neurologist diagnosed the patient as having had a transient ischemic attack (TIA), even though the episode lasted for a couple of days. She recounted similar, albeit smaller episodes, a few months prior to my consultation. A computed tomography scan revealed no space-occupying lesion or focal abnormalities and the electroencephalogram result was normal. Physical examination revealed no abnormalities or neurologic deficits. She had difficulty remembering three words that I asked her to repeat five minutes later. I explained to the patient that I wasn't sure about her diagnosis. I mentioned that her vitamin B_{12} status might be implicated in the genesis of her neurologic symptoms.

The patient's serum vitamin B_{12} result was 290 pg/mL (214 pmol/L) and not optimal according to my standards. I administered an IM injection of 1,000 mcg hydroxocobalamin and told the patient to return in 10 days for another injection. A second injection was given, but this time the dose was increased to 1,500 mcg. About one month after the initial consultation (end of February), the patient returned for a third injection. She felt about 80% better, and noticed that she could remember events and articulate her thoughts better. Other symptoms remitted as well, which included numbness, tingling, and dizziness. She was given another injection of 1,500 mcg during the visit. She returned in early March for a follow-up visit. She maintained her 80% improvement level and was given another injection at 1,000 mcg of hydroxocobalamin. She also brought serum vitamin B_{12} results from another clinician, and her level increased to greater than 2,000 pg/mL (1,476 pmol/L) since commencing treatment.

About one month later, in early April, the patient returned for another visit. She noticed a regression of her symptoms by about 20%, as her speech issues were return-

ing. I gave the patient an injection of 1,500 mcg (1,000 mcg hydroxocobalamin and 500 mcg methylcobalamin). Two weeks later, she came in for another injection and felt back to her original improvement level. Since that time, the patient comes every two weeks and feels that her symptoms are kept at bay from receiving IM injections of vitamin B_{12}. It should also be noted that the patient had symptoms of mild anxiety when she first presented. She scored a 14 on the BAI, placing her in the "mild anxiety" category. About 5 weeks after vitamin B_{12} therapy commenced, her BAI score decreased to a 6, which is essentially normal.

Conclusion

Clinicians may wish to re-evaluate the importance of lower-than-optimal serum vitamin B_{12} levels, pursue additional testing such as uMMA, and consider the potential benefits of vitamin B_{12} treatment.

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January 26, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA, NCPA, IACP and Fagron as nominators of methylcobalamin for inclusion on the 503A Bulk Drug Substances list. Below are our responses to FDA's questions #1 and #2.

1. The above signatories do want to pursue review by the FDA and consideration by the PCAC of methylcobalamin for inclusion on the 503A Bulks list.
2. While there is clinical literature about the positive efficacy for methylcobalamin in a variety of disease states, the primary patient need for compounded methylcobalamin is for patients with Autism Spectrum Disorders.

Proposed Use	Scientific Literature	Dosage Form & Strength/Concentration
Autism Spectrum Disorders	Frye RE, Melnyk S, Fuchs G, et al. *Autism Res Treat*. 2013;2013:609705.	Injectable solution 0.5 mg/mL to 12.5 mg/mL
	Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. *J Child Adolesc Psychopharmacol.* 2016 Nov, 26(9):774-783. https://doi.org/10.1089/cap.2015.0159	
	James SJ, Melnyk S, Fuchs G, et al. *Am J Clin Nutr*. 2009;89(1):425-30.	
	James SJ, Cutler P, Melnyk S, et al. *Am J Clin Nutr.* 2004 Dec;80(6):1611-7.	

We look forward to providing you further information as requested in the coming weeks.

Sincerely,

Jim Smith
PCCA President

Ronna Hauser, PharmD
NCPA Vice President of Pharmacy Affairs

Erik Tosh, BS, DPh, FIACP, FACA
IACP President

Alex Govze
Fagron Legal Counsel

February 22, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA, NCPA, IACP and Fagron as nominators of methylcobalamin for inclusion on the 503A Bulk Drug Substances list. Given the relatively short timelines in FDA's request, the information provided here is not to be considered all-inclusive. Some clinicians may have further information that we were not able to collect by the due date requested. Also, please note that methylcobalamin does have a USP monograph, and thus meets the statutory requirements for use as an Active Pharmaceutical Ingredient under section 503A of the DQSA.

Below are our responses to FDA's questions #3 and #4:

3. To the best of our abilities, approximately 250,000 prescriptions of compounded methylcobalamin per year are estimated to be dispensed in the treatment of autism spectrum disorders (ASD).

4. At the Defeat Autism Now! (DAN!) 2004 conference, methylcobalamin was awarded "most recommended medical treatment" for ASD by the attending DAN! doctors for the year.

   The Medical Academy of Pediatric Special Needs (MAPS) and Autism Speaks currently teach, provide research grants, and advocate for the use of compounded methylcobalamin in the treatment of their patients. MAPS utilizes only evidence-based medicine related to the care of patients with ASD. Their curriculum covers numerous clinical trials addressing FDA-approved drugs, non-FDA approved drugs, nutritional therapies and behavioral therapies. Methylcobalamin is a vital component of their recommended treatment regimen. The clinical trials in this patient population suggests adverse events are extremely rare and are generally limited to injection site reaction.

   Additionally, the following references discuss the clinical role of methylcobalamin in patients with ASD:

- mB12 taken by SC injection and orally were rated as #2 and #4 of the top 20 complementary and alternative medicine therapies used by children with ASD in an Autism Research Institute study which ranked data from more than 26,000 parental surveys (Rossignol 2009). In our online parental survey of treatments used for ASD we found that methylcobalamin was the top-rated non-traditional medical treatment (Frye, Sreenivasula et al. 2011).

- Because of the large number of children with ASD who have gastrointestinal problems and the fact that some children with ASD are believed to have a central cobalamin deficiency thus requiring high blood levels of cobalamin to cross the blood brain barrier (Frye, Delhey et al. 2016, Zhang, Hodgson et al. 2016), it is reasonable to hypothesize that SC injected mB12 is more effective than oral administration.

It is important to note that methylcobalamin is not a cure for autism or autism spectrum disorders. There are no cures for these complex conditions. Methylcobalamin does significantly improve core symptoms in many of these patients, which often allows the patients to be higher functioning individuals. These symptoms include, but are not limited to, language and vocalization, social behavior and sleep.

The only FDA-approved therapies for ASD are aripiprazole and risperidone, which have significant adverse event profiles, and only address secondary symptoms of irritability. The underlying core symptoms are not addressed with these therapies.

We hope this information aids the Agency in your review of compounded methylcobalamin. If you require further information, please contact us at your convenience.

Sincerely,

Jim Smith
PCCA President

Ronna Hauser, PharmD
NCPA Vice President of Pharmacy Affairs

Erik Tosh, BS, DPh, FIACP, FACA
IACP President

Alex Govze
Fagron Legal Counsel

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Jan. 26, 2018

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903
Email: toni.hallman@fda.hhs.gov

RE: Docket FDA-2015-N-3534, Methylcobalamin

Dear Ms. Hallman,

McGuff Compounding Pharmacy Services, Inc. (MCPS) is responding to the FDA's questions to the nomination of Methylcobalamin inclusion on the 503A bulk drug substances list due by Jan. 26, 2018.

Responses:

Q. Does MCPS still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulk list?
A. Yes.

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide scientific articles supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.
A. The compounded dosage form is a parenteral injection ranging from 1 mg/mL to 5mg/mL for all listed uses for methylcobalamin below:

Austistic Spectrum Disorder

a. "Treatments for biomedical abnormalities associated with autism spectrum disorder." R.E. Frye, June 2014.
b. "Effectiveness of Methylcobalamin and Folinic Acid Treatment on Adaptive Behavior in Children with Autistic Disorder Is Related to Glutathione Redox Status."

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

Diabetic Neuropathy

c. "Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials." Sun Y.
d. "Intravenous Methylcobalamin Treatment for Uremic Diabetic Neuropathy in Chronic Hemodialysis Patients." S. Kuwabara 1999.
e. "Potential Benefits of Methylcobalamin: A Review." Gupta JK et al, 2015.

Pain Management

f. "Intravenous and Intrathecal Methylcobalamin: A Potential Vitamin of Pain Killer." Zhang 2016.

Amyotrophic Lateral Sclerosis

g. Amyotrophic Lateral Sclerosis: phase 3 clinical study.
h. "Potential Benefits of Methylcobalamin: A Review." Gupta JK et al, 2015.

Conjunctive Therapy In Hemodialysis Patients

i. "Efficacy of methylcobalamin on lowering homocysteine plasma concentrations in haemodialysis patients receiving high dose folic acid supplementation." Koyama K et al, 2002.

Please let us know if you are in need of any further information.

Sincerely,

Ronald M. McGuff, President/CEO
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., STE 142
Santa Ana, CA 92704

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Treatments for biomedical abnormalities associated with autism spectrum disorder

***Richard Eugene Frye*[1]* and Daniel A. Rossignol*[2]**

[1] *Department of Pediatrics, Arkansas Children's Hospital Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[2] *Rossignol Medical Center, Irvine, CA, USA*

Edited by:
Roberto Canitano, University Hospital of Siena, Italy

Reviewed by:
Andrew Walter Zimmerman, Harvard Medical School, USA
Robert Hendren, University of California San Francisco, USA

***Correspondence:**
Richard Eugene Frye, Arkansas Children's Hospital Research Institute, Slot 512-41B, 13 Children's Way, Little Rock, AR 72202, USA
e-mail: refrye@uams.edu

Recent studies point to the effectiveness of novel treatments that address physiological abnormalities associated with autism spectrum disorder (ASD). This is significant because safe and effective treatments for ASD remain limited. These physiological abnormalities as well as studies addressing treatments of these abnormalities are reviewed in this article. Treatments commonly used to treat mitochondrial disease have been found to improve both core and associated ASD symptoms. Double-blind, placebo-controlled (DBPC) studies have investigated L-carnitine and a multivitamin containing B vitamins, antioxidants, vitamin E, and co-enzyme Q10 while non-blinded studies have investigated ubiquinol. Controlled and uncontrolled studies using folinic acid, a reduced form of folate, have reported marked improvements in core and associated ASD symptoms in some children with ASD and folate related pathway abnormities. Treatments that could address redox metabolism abnormalities include methylcobalamin with and without folinic acid in open-label studies and vitamin C and *N*-acetyl-L-cysteine in DBPC studies. These studies have reported improved core and associated ASD symptoms with these treatments. Lastly, both open-label and DBPC studies have reported improvements in core and associated ASD symptoms with tetrahydrobiopterin. Overall, these treatments were generally well-tolerated without significant adverse effects for most children, although we review the reported adverse effects in detail. This review provides evidence for potentially safe and effective treatments for core and associated symptoms of ASD that target underlying known physiological abnormalities associated with ASD. Further research is needed to define subgroups of children with ASD in which these treatments may be most effective as well as confirm their efficacy in DBPC, large-scale multicenter studies.

Keywords: autism spectrum disorders, mitochondria, folate receptor alpha, folinic acid, folate metabolism, redox regulation, oxidative stress, tetrahydrobiopterin

BACKGROUND

The autism spectrum disorders (ASD) are a group of behaviorally defined neurodevelopmental disorders with lifelong consequences. They are defined by impairments in communication and social interaction along with restrictive and repetitive behaviors (1). The definition of ASD has recently undergone revision. Previously, the Diagnostic Statistical Manual (DSM) Version IV Text Revision divided ASD into several diagnoses including autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified. The new revision of the DSM now does not differentiate between these ASD subtypes and considers communication and social impairments together in one symptom class (2). Complicating this change is the fact that over the past several decades, most research has used a framework from the former DSM versions.

Autism spectrum disorder has been recently estimated to affect 1 out of 68 individuals in the United States (3) with four times more males than females being affected (4). Over the past two decades, the prevalence of the ASDs has grown dramatically, although the reasons for this increase are continually debated. Despite decades of research on ASD, identification of the causes of and treatments for ASD remain limited. The standard-of-care treatment for ASD is behavioral therapy that requires full-time engagement of a one-on-one therapist typically requiring many years of treatment, and recent reviews have pointed out that controlled studies on commonly used behavior therapies are generally lacking (5). The only medical treatments approved by the United States of America Food and Drug Administration for ASD are antipsychotic medications. However, these medications only treat a symptom associated with ASD, irritability, but not any core ASD symptom. In children, these medications can be associated with significant adverse effects, including detrimental changes in body weight as well as triglyceride, cholesterol, and blood glucose concentrations within a short time (6) and they also increase the risk of type 2 diabetes (7). In some studies, the percentage of children experiencing these side effects is quite high. For example, one recent study reported that 87% of ASD children had side effects with risperidone, including drowsiness, weight gain, and rhinorrhea (8).

A great majority of ASD research has concentrated on genetic causes of ASD (9) despite the fact that inherited single gene and chromosomal defects are only found in the minority of cases

(10). In fact, several recent studies that have conducted genome wide searches for common genetic defects across large samples of ASD children have only identified rare *de novo* mutations, thereby pointing to acquired mutations and/or mutations secondary to errors in DNA maintenance rather than inherited genetic syndromes (11, 12). As research in the field of ASD continues, it is becoming clear that the etiology of most ASD cases involves complicated interactions between genetic predisposition and environmental exposures or triggers. Indeed, a recent study of dizygotic twins estimated that the environment contributes a greater percentage of the risk of developing autistic disorder as compared to genetic factors (13). Another study of over two million children reported that environmental risk factors accounted for approximately 50% of ASD risk (14). Recent reviews have outlined the many environmental factors that are associated with ASD and have described how polymorphisms in specific genes can combine with the environment to cause neurodevelopmental problems (15).

Recent studies have suggested that ASD is associated with impairments in basic physiological processes such as redox (16) and mitochondrial (9) metabolism as well as abnormalities in regulating essential metabolites such as folate (17), tetrahydrobiopterin (18–20), glutathione (21–23), cholesterol (24), carnitine (25–28), and branch chain amino acids (29). Although many of these studies have based their findings on peripheral markers of abnormal metabolism, many studies have documented some of these same abnormalities in the brain of individuals with ASD, including mitochondrial dysfunction and oxidative stress (30) and one study has demonstrated a link between oxidative stress, inflammation, and mitochondrial dysfunction in the brain of individuals with ASD (23). Interestingly, several of these physiological abnormalities are also observed in genetic syndromes associated with ASD. For example, mitochondrial dysfunction is prevalent in both idiopathic ASD (31) and is associated with Rett syndrome (32–34), PTEN mutations (35), Phelan-McDermid syndrome (36), 15q11-q13 duplication syndrome (37, 38), Angelman syndrome (39), Septo-optic dysplasia (40), and Down syndrome (41, 42).

Identifying the metabolic or physiological abnormalities associated with ASD is important, as treatments for such abnormalities may be possible. Thus, a better understanding of these abnormalities may allow for the development of novel treatments for children with ASD. Below the evidence for metabolic abnormalities related to ASD that may be amenable to treatment are discussed along with the evidence of potential treatments for these disorders. **Figure 1** provides a summary of the pathways and demonstrates which pathways are targeted by the better studied treatments. In addition, a section on the common adverse effects of these treatments follows the discussion of treatments.

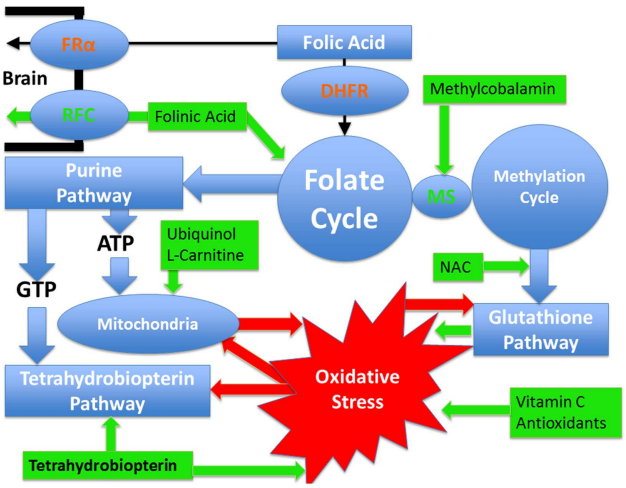

FIGURE 1 | Pathways affected in autism spectrum disorder that are discussed in this article as well as the treatments discussed with their points of action. Pathways are outlined in blue while treatments are outlined in green. Oxidative stress is outlined in red and the red arrows demonstrate how it can negatively influence metabolic pathways. Certain pathways such as glutathione and tetrahydrobiopterin pathways have an antioxidant effect and a reciprocal relationship with oxidative stress such that they can improve oxidative stress but at the same time oxidative stress has a direct detrimental effect on them. Mitochondrial dysfunction and oxidative stress have mutually negative effects on each other such that oxidative stress causes mitochondrial dysfunction while mitochondrial dysfunction worsens oxidative stress. Dihydrofolate reductase (DHFR) is colored in red since polymorphisms in this gene, that are commonly seen in individuals with autism, have a detrimental effect on the reduction of folic acid such that the entry of folic acid into the folate cycle is decreased. Folinic acid enters the folate cycle without requiring this enzyme. Similarly the folate receptor alpha can be impaired in individuals with autism by autoantibodies and by mitochondrial dysfunction. In such cases, folinic acid can cross the blood–brain barrier by the reduced folate carrier. Methionine synthase (MS) connects the folate and methylation cycles and requires methylcobalamin as a cofactor.

REVIEW OF TREATABLE CONDITIONS AND THEIR POTENTIAL TREATMENTS

MITOCHONDRIAL DYSFUNCTION

Recent studies suggested that 30–50% of children with ASD possess biomarkers consistent with mitochondrial dysfunction (31, 43) and that the prevalence of abnormal mitochondrial function in immune cells derived from children with ASD is exceedingly high (44, 45). Mitochondrial dysfunction has been demonstrated in the postmortem ASD brain (23, 30, 46–49) and in animal models of ASD (50). Novel types of mitochondrial dysfunction have been described in children with ASD (28, 51, 52) and in cell lines derived from children with ASD (53, 54). Several studies suggest that children with ASD and mitochondrial dysfunction have more severe behavioral and cognitive disabilities compared with children who have ASD but without mitochondrial dysfunction (55–57). Interestingly, a recent review of all of the known published cases of mitochondrial disease and ASD demonstrated that only about 25% had a known genetic mutation that could account for their mitochondrial disease (31).

Treatments that are typically used for patients with mitochondrial disease have been shown to improve functioning in some children with ASD (31). Several studies, including two double-blind, placebo-controlled (DBPC) studies (58, 59) and case reports (25, 37, 60–63) have reported improvements in core and associated ASD behaviors with L-carnitine treatment. Two DBPC studies using a multivitamin containing B vitamins, antioxidants, vitamin E, and co-enzyme Q10 reported various

improvements in ASD symptoms compared to placebo (64, 65). Several other antioxidants (66), including vitamin C (67), methylcobalamin (68–70), *N*-acetyl-L-cysteine (71–73), ubiquinol (74), and carnosine (75), have also reported to demonstrate significant improvements in ASD behaviors and may function to improve mitochondrial function.

Thus, many treatments that are believed to improve mitochondrial function have been shown to be helpful for some children with ASD. However, none of these studies have specifically selected children with mitochondrial dysfunction or disease to study, so it is difficult to know if individuals with ASD and mitochondrial dysfunction would benefit the most from these treatments or whether these treatments are effective for a wider group of children with ASD. One study did demonstrate that the multivitamin used for treatment resulted in improvements in biomarkers of energy metabolism (as well as oxidative stress) suggesting that the effect of the multivitamin may have been at least partially related to improvements in mitochondrial function (65). Clearly, this is a fertile area for research but there remain several complications that could impede moving forward in a systematic way. For example, given the inconsistency in the prevalence estimates of mitochondrial disease and dysfunction across studies (ranging from about 5–80%), the notion that mitochondrial abnormalities are even associated with ASD is somewhat controversial. This may be, in part, due to the unclear distinction between mitochondrial disease and dysfunction. However, even the lower bound of the prevalence estimate of 5% is significant, as mitochondrial disease is only believed to affect <0.1% of individuals in the general population and given the current high prevalence of ASD, a disorder that affects even 5% of individuals with ASD would add up to millions of individuals who have the potential to have a treatable metabolic abnormality. Other complicating factors include the fact that there are many treatments for mitochondrial disease and these treatments have not been well-studied (76). Hopefully, the increased interest in treatments for mitochondrial disease will help improve our knowledge of how to best treat mitochondrial disease so that such information can be applied to children who have mitochondrial disease and dysfunction with ASD. Other recent approaches include the *in vitro* assessment of compounds that may improve mitochondrial function in individuals with ASD (53).

FOLATE METABOLISM

Several lines of evidence point to abnormalities in folate metabolism in ASD. Several genetic polymorphisms in key enzymes in the folate pathway have been associated with ASD. These abnormalities can cause decreased production of 5-methyltetrahydrofolate, impair the production of folate cycle metabolites and decrease folate transport across the blood–brain barrier and into neurons. Indeed, genetic polymorphisms in methylenetetrahydrofolate reductase (22, 77–85), dihydrofolate reductase (86) and the reduced folate carrier (22) have been associated with ASD.

Perhaps the most significant abnormalities in folate metabolism associated with ASD are autoantibodies to the folate receptor alpha (FRα). Folate is transported across the blood–brain barrier by an energy-dependent receptor-mediated system that utilizes the FRα (87). Autoantibodies can bind to the FRα and greatly impair its function. These autoantibodies have been linked to cerebral folate deficiency (CFD). Many cases of CFD carry a diagnosis of ASD (88–94) and other individuals with CFD are diagnosed with Rett syndrome, a disorder closely related to ASD within the pervasive developmental disorder spectrum (95–97). Given that the FRα folate transport system is energy-dependent and consumes ATP, it is not surprising that a wide variety of mitochondrial diseases (91, 94, 97–102) and novel forms of mitochondrial dysfunction related to ASD (52) have been associated with CFD. Recently, Frye et al. (17) reported that 60% and 44% of 93 children with ASD were positive for the blocking and binding FRα autoantibody, respectively. This high rate of FRα autoantibody positivity was confirmed by Ramaekers et al. (103) who compared 75 ASD children to 30 non-autistic controls with developmental delay. The blocking FRα autoantibody was positive in 47% of children with ASD but in only 3% of the control children.

Many children with ASD and CFD have marked improvements in clinical status when treated with folinic acid – a reduced form of folate that can cross the blood–brain barrier using the reduced folate carrier rather than the FRα transport system. Several case reports (89) and case series (90, 91) have described neurological, behavioral, and cognitive improvements in children with documented CFD and ASD. One case series of five children with CFD and low-functioning autism with neurological deficits found complete recovery from ASD symptoms with the use of folinic acid in one child and substantial improvements in communication in two other children (90). In another study of 23 children with low-functioning regressive ASD and CFD, 2 younger children demonstrated full recovery from ASD and neurological symptoms, 3 older children demonstrated improvements in neurological deficits but not in ASD symptoms, and the remainder demonstrated improvements in neurological symptoms and partial improvements in some ASD symptoms with folinic acid; the most prominent improvement was in communication (91). Recently, in a controlled open-label study, Frye et al. (17) demonstrated that ASD children who were positive for at least one of the FRα autoantibodies experienced significant improvements in verbal communication, receptive and expressive language, attention, and stereotypical behavior with high-dose (2 mg/kg/day in two divided doses; maximum 50 mg/day) folinic acid treatment with very few adverse effects reported.

Thus, there are several lines of converging evidence suggesting that abnormalities in folate metabolism are associated with ASD. Evidence for treatment of these disorders is somewhat limited but it is growing. For example, treatment studies have mostly concentrated on the subset of children with ASD who also possess the FRα autoantibodies. These studies have only examined one form of reduced folate, folinic acid, and have only examined treatment response in limited studies. Thus, large DBPC studies would be very helpful for documenting efficacy of this potentially safe and effective treatment. In addition, the role of other abnormalities in the folate pathway beside FRα autoantibodies, such as genetic polymorphisms, in treatment response needs to be investigated. It might also be important to investigate the role of treatment with other forms of folate besides folinic acid, but it might also be wise to concentrate research on one particular form of folate for the time being so as to optimize the generalizability of research studies in order to have a more solid understanding of the role of folate

metabolism in ASD. Given the ubiquitous role of folate in many metabolic pathways and the fact that it has a role in preventing ASD during the preconception and prenatal periods (104), this line of research has significant potential for being a novel treatment for many children with ASD.

REDOX METABOLISM

Several lines of evidence support the notion that some children with ASD have abnormal redox metabolism. Two case-control studies have reported that redox metabolism in children with ASD is abnormal compared to unaffected control children (22, 105). This includes a significant decrease in reduced glutathione (GSH), the major intracellular antioxidant, and mechanism for detoxification, as well as a significant increase in the oxidized disulfide form of glutathione (GSSG). The notion that abnormal glutathione metabolism could lead to oxidative damage is consistent with studies which demonstrate oxidative damage to proteins and DNA in peripheral blood mononuclear cells and postmortem brain from ASD individuals (23, 30, 106), particularly in cortical regions associated with speech, emotion, and social behavior (30, 107).

Treatments for oxidative stress have been shown to be of benefit for children with ASD. In children with ASD, studies have demonstrated that glutathione metabolism can be improved with subcutaneously injected methylcobalamin and oral folinic acid (69, 105), a vitamin and mineral supplement that includes antioxidants, co-enzyme Q10, and B vitamins (65) and tetrahydrobiopterin (20). Interestingly, recent DBPC studies have demonstrated that *N*-acetyl-L-cysteine, a supplement that provides a precursor to glutathione, was effective in improving symptoms and behaviors associated with ASD (72, 73). However, glutathione was not measured in these two studies.

Small (64, 67), medium (72, 73), and large (108) sized DPBC trials and small and medium-sized open-label clinical trials (68, 70) demonstrate that novel treatments for children with ASD, which can address oxidative stress are associated with improvements in core ASD symptoms (68, 70, 72), sleep and gastrointestinal symptoms (64), hyperactivity, tantruming, and parental impression of general functioning (108), sensory-motor symptoms (67), and irritability (72, 73). These novel treatments include *N*-acetyl-L-cysteine (72, 73), methylcobalamin with (69, 70) and without (68) oral folinic acid, vitamin C (67), and a vitamin and mineral supplement that includes antioxidants, co-enzyme Q10, and B vitamins (64, 65).

Several other treatments that have antioxidant properties (66), including carnosine (75), have also been reported to significantly improve ASD behaviors, suggesting that treatment of oxidative stress could be beneficial for children with ASD. Many antioxidants can also help improve mitochondrial function (31), suggesting that clinical improvements with antioxidants may occur through a reduction of oxidative stress and/or an improvement in mitochondrial function.

These studies suggest that treatments that address oxidative stress may improve core and associated symptoms of ASD. Furthermore, these treatments are generally regarded as safe with a low prevalence of adverse effects. Unfortunately many studies that have looked at antioxidants and treatments that potentially support the redox pathway did not use biomarkers to measure redox metabolism status in the participants or the effect of treatment on redox pathways. Including biomarkers in future studies could provide important information regarding which patients may respond to treatments that address redox metabolism and can help identify the most effective treatments. Since there are many treatments used to address oxidative stress and redox metabolism abnormalities in clinical practice and in research studies, the most effective treatments need to be carefully studied in DBPC studies to document their efficacy and effectiveness. Overall, the treatments discussed above have shown some promising results and deserve further study.

TETRAHYDROBIOPTERIN METABOLISM

Tetrahydrobiopterin (BH_4) is a naturally occurring molecule that is an essential cofactor for several critical metabolic pathways, including those responsible for the production of monoamine neurotransmitters, the breakdown of phenylalanine, and the production of nitric oxide (19). BH_4 is readily oxidized by reactive species, leading it to be destroyed in the disorders where oxidative stress is prominent such as ASD (18). Abnormalities in several BH_4 related metabolic pathways or in the products of these pathways have been noted in some individuals with ASD, and the cerebrospinal fluid concentration of BH_4 has been reported to be depressed in some individuals with ASD (19). Clinical trials conducted over the past 25 years have reported encouraging results using sapropterin, a synthetic form of BH_4, to treat children with ASD (19). Three controlled (109–111) and several open-label trials have documented improvements in communication, cognitive ability, adaptability, social abilities, and verbal expression with sapropterin treatment in ASD, especially in children younger than 5 years of age and in those who are relatively higher functioning at the beginning of the trial (19).

Frye has shown that the ratio of serum citrulline-to-methionine is related to the BH_4 concentration in the cerebrospinal fluid, suggesting that abnormalities in both oxidative stress and nitric oxide metabolism may be related to central BH_4 deficiency (18). More recently, Frye et al. demonstrated, in an open-label study, that sapropterin treatment improves redox metabolism and fundamentally alters BH_4 metabolism in children with ASD. Interestingly, serum biomarkers of nitric oxide metabolism were found to predict response to sapropterin treatment in children with ASD (20), thereby suggesting that the therapeutic effect of BH_4 supplementation may be specific to its effect on nitric oxide metabolism.

The potential positive effects on nitric oxide metabolism by BH_4 supplementation could be significant for several reasons. The literature supports an association between ASD and abnormalities in nitric oxide metabolism. Indeed studies have documented alterations in nitric oxide synthase genes in children with ASD (112, 113). In the context of low BH_4 concentrations, nitric oxide synthase produces peroxynitrite, an unstable reactive nitrogen species that can result in oxidative cellular damage. Indeed, nitrotyrosine, a biomarker of reactive nitrogen species, has been shown to be increased in multiple tissues in children with ASD, including the brain (22, 23, 107, 114, 115). Thus, BH_4 supplementation could help stabilize nitric oxide synthase as well as act as an antioxidant and improve monoamine neurotransmitter production. Further

DBPC studies using biomarkers of metabolic pathways related to BH_4 metabolism will be needed to determine which children with ASD will most benefit from formulations of BH_4 supplementation like sapropterin.

POTENTIAL ADVERSE EFFECTS

Although many of the treatments discussed within this manuscript are considered safe and are generally well-tolerated, it is important to understand that these treatments are not without potential adverse effects. In general, these treatments are without serious adverse effects but some children may not tolerate all treatments well. Systematic and controlled studies are best at providing data on adverse effects, so the true adverse effects of the supplements discussed will only be based on the limited treatments that have been studied in such a fashion. It is also important to understand that because of the complicated nature of the effects of these treatments, they should only be used under the care of a medical professional with appropriate expertise and experience.

Controlled studies for treatments that address mitochondrial disorders include L-carnitine and a multivitamin with various mitochondrial supplements. In one small DBPC study, there were no significant adverse events reported in the 16 children treated with L-carnitine (59) while a second small DBPC trial reported no differences between the adverse effects reported by the treatment and placebo groups; notably, more patients in the placebo group withdrew from the study because of adverse effects (58). Thus, there is no data to suggest that L-carnitine has any significant adverse effects. In the large DBPC multivitamin study, about equal numbers of children in the treatment and placebo groups withdrew from the study because of behavior or gastrointestinal issues (65). In another small DBPC study, the investigators noted that two children began to have nausea and emesis when they started receiving the treatment at nighttime on an empty stomach (64). This adverse effect resolved when the timing of the treatment was adjusted. Thus, with proper dosing of this multivitamin, it appears rather safe and well-tolerated.

Controlled studies for folate pathway abnormalities only include folinic acid. In a medium-sized, open-label controlled study, 44 children with ASD and the FRα autoantibody were treated with high-dose folinic acid (2 mg/kg/day in two divided doses; maximum 50 mg/day) and four children discontinued the treatment because of an adverse effect (17). Of the four children who discontinued the treatment, three children, all being concurrently treated with risperidone, demonstrated increased irritability soon after starting the high-dose folinic acid while the other child experienced increased insomnia and gastroesophageal reflux after 6 weeks of treatment. Since there was no placebo in this study, the significance of these adverse effects is difficult to determine. For example, it is not clear whether this was related to concurrent risperidone treatment or was related to a baseline high irritability resulting in the needed for risperidone. All other participants completed the trial without significant adverse effects. Due to the timing of the adverse events in the children on risperidone in this trial, to be safe, the authors suggested caution when using folinic acid in children already on antipsychotic medications.

Clinical studies for treatments that could address redox metabolism include *N*-acetyl-L-cysteine, methylcobalamin, methylcobalamin combined with oral folinic acid and a multivitamin (as previous mentioned). One small open-label study that provided 25–30 μg/kg/day (1500 μg/day maximum) of methylcobalamin to 13 patients found no adverse effects (68) while a medium-sized, open-label trial that provided 75 μg/kg subcutaneously injected methylcobalamin given every 3 days along with twice daily oral low-dose (800 μg/day) folinic acid to 44 children noted some mild adverse effects (69, 70). Four children discontinued the treatment, two because their parents were uncomfortable given injections and two because of hyperactivity and reduced sleep. The most common adverse effect in the participants that remained in the study was hyperactivity, which resolved with a decrease in the folinic acid to 400 μg/day. Lastly, two medium sized, DBPC studies examined *N*-acetyl-L-cysteine, one as a primary treatment and another as an add-on to risperidone. The trial that used *N*-acetyl-L-cysteine as a primary treatment noted no significant differences in adverse events between the treatment and placebo groups, although both groups demonstrated a high rate of gastrointestinal symptoms and one participant in the active treatment phase required termination due to increased agitation (72). In the add-on study, one patient in the active treatment group withdrew due to severe sedation (73). In this latter study, adverse effects were not compared statistically between groups, but most adverse effects were mild and had a low prevalence. Such adverse effects included constipation, increased appetite, fatigue, nervousness, and daytime drowsiness. Lastly, a small DPBC study using vitamin C did not report any adverse effects from the treatment (67). Thus, there are several relatively safe and well-tolerated treatments for addressing abnormal redox metabolism, but there does appear to be a low rate of adverse effects, reinforcing the notion that a medical professional should guide treatment.

Three DBPC studies, one small (110), one medium (111), and one medium-to-large (109) sized, were conducted using sapropterin as a treatment for ASD. None of these studies have reported a higher prevalence of adverse effects in the treatment group as compared to the placebo group and none of these studies attributed any dropouts to the treatment. Thus, sapropterin appears to be a well-tolerated treatment.

DISCUSSION

One advantage of the treatments outlined above is that the physiological mechanisms that they address are known and biomarkers are available to identify children who may respond to these treatments. Preliminary studies suggest that there are a substantial number of ASD children with these metabolic abnormalities. For example, mitochondrial abnormalities may be seen in 5–80% of children with ASD (31, 43–45, 53, 54) and FRα autoantibodies may be found in 47% (103) to 75% (17) of children with ASD. Clearly, further studies will be required to clarify the percentage of these subgroups.

Further large-scale, multicenter DBPC clinical trials are needed for these promising treatments in order to document the efficacy and define the subgroups that best respond to these treatments. As more treatable disorders are documented and as data accumulates to demonstrate the efficacy of treatments for these disorders, clinical algorithms to approach the work-up for a child with ASD need to be developed by a consensus of experts. Indeed, developing

guidelines will be the next step for applying many of these scientific findings. Clearly many children with ASD may be able to benefit from such treatments, which are focused on improving dysfunctional physiology. Given the fact that no approved medical treatment exists which addresses the underlying pathophysiology or core symptoms of ASD, these treatments could make a substantial difference in the lives of children with ASD and their families. With the high prevalence of ASD, treatments that successfully treat even only a fraction of children affected with ASD would translate into substantial benefits for millions of individuals with ASD and their families. In summary, it appears that many of these treatments may provide benefit for a substantial proportion of children with ASD.

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Clinical Study

Effectiveness of Methylcobalamin and Folinic Acid Treatment on Adaptive Behavior in Children with Autistic Disorder Is Related to Glutathione Redox Status

Richard E. Frye,[1] Stepan Melnyk,[1] George Fuchs,[1] Tyra Reid,[1] Stefanie Jernigan,[1] Oleksandra Pavliv,[1] Amanda Hubanks,[1] David W. Gaylor,[2] Laura Walters,[1] and S. Jill James[1]

[1] *Department of Pediatrics, Arkansas Children's Hospital Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR 72202, USA*
[2] *Department of Biostatistics, Arkansas Children's Hospital Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR 72202, USA*

Correspondence should be addressed to Richard E. Frye; refrye@uams.edu

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Treatments targeting metabolic abnormalities in children with autism are limited. Previously we reported that a nutritional treatment significantly improved glutathione metabolism in children with autistic disorder. In this study we evaluated changes in adaptive behaviors in this cohort and determined whether such changes are related to changes in glutathione metabolism. Thirty-seven children diagnosed with autistic disorder and abnormal glutathione and methylation metabolism were treated with twice weekly 75 μg/Kg methylcobalamin and twice daily 400 μg folinic acid for 3 months in an open-label fashion. The Vineland Adaptive Behavior Scale (VABS) and glutathione redox metabolites were measured at baseline and at the end of the treatment period. Over the treatment period, all VABS subscales significantly improved with an average effect size of 0.59, and an average improvement in skills of 7.7 months. A greater improvement in glutathione redox status was associated with a greater improvement in expressive communication, personal and domestic daily living skills, and interpersonal, play-leisure, and coping social skills. Age, gender, and history of regression did not influence treatment response. The significant behavioral improvements observed and the relationship between these improvements to glutathione redox status suggest that nutritional interventions targeting redox metabolism may benefit some children with autism.

1. Introduction

Autism is a neurodevelopmental disorder characterized by significant impairment in reciprocal social interaction and communication as well as restricted interests and repetitive behaviors. An estimated 1 of 88 individuals in the United States is affected with an autism spectrum disorder (ASD) [1]. Although several genetic syndromes are associated with ASD, all of these genetic syndromes together only account for a minority of ASD cases [2]. Other areas of novel research have concentrated on systemic physiological abnormalities, such as mitochondrial dysfunction [3, 4], oxidative stress [5–7], and inflammation/immune dysregulation [8–10]. These novel areas of research have substantially grown over the last decade [11]. These emerging areas of research have provided a new understanding of the diverse mechanisms involved in ASD and have promoted the idea that the autism spectrum is composed of several subgroups or endophenotypes [12].

Several lines of evidence support the notion of an ASD endophenotype with abnormal redox and methylation metabolism. In two case-control studies we reported that redox and methylation metabolism in children diagnosed with autism was abnormal compared to that of unaffected control children [6, 13]. Briefly, the mean ratio of plasma S-adenosyl methionine (SAM) to S-adenosyl homocysteine (SAH), a reflection of cellular methylation capacity, was

significantly reduced. Also, the mean concentration of free reduced glutathione (GSH), the major intracellular antioxidant and mechanism for detoxification, was also significantly decreased and the oxidized disulfide form of glutathione (GSSG) was significantly increased. This imbalance in reduced as compared to oxidized glutathione resulted in a 2-fold reduction in the GSH/GSSG redox ratio, an index known as the glutathione redox status. Several precursors for methylation and glutathione synthesis were also lower in the autistic children suggesting an insufficiency in the production of methylation and glutathione metabolites, at least in a subgroup of ASD children. In addition, we have also demonstrated that GSH is significantly reduced in the cytosol and isolated mitochondria from lymphoblastoid cell lines and fresh peripheral blood mononuclear cells derived from children with autistic disorder (AD) [14, 15].

The glutathione provides the essential intracellular reducing environment required for normal immune function, detoxification capacity, redox-sensitive enzyme activity, and membrane redox signaling [16–20]. Oxidative stress occurs when antioxidant defense mechanisms fail to counterbalance reactive oxygen species generated from endogenous oxidative metabolism or from prooxidant environmental exposures. The notion that abnormal glutathione metabolism is associated with oxidative cellular damage is consistent with studies from our laboratory which demonstrate an increase in oxidative damage to protein and DNA in peripheral blood mononuclear cells and postmortem brain derived from ASD individuals [15, 21]. Several recent reviews and research studies also lend support to the hypothesis that redox imbalance and oxidative stress may be a contributing factor to autism pathophysiology [6, 22].

These findings have particular clinical relevance since abnormalities in redox metabolism are potentially amenable to treatment. Glutathione is a tripeptide of cysteine, glycine, and glutamate that is synthesized *de novo* in all cells. Glutathione synthesis is tightly connected to methylation metabolism where it derives its cysteine precursor. As both methylation and glutathione metabolism have been shown to be abnormal in children with ASD and due to the fact that abnormal methylation metabolism will result in a depletion of the precursors needed for glutathione production, we previously conducted an open-label intervention trial where targeted metabolic cofactors for methylation and glutathione metabolism were provided. Specifically, in our previous study, we determine if glutathione redox status could be improved with a three-month intervention of subcutaneously injected methylcobalamin and oral folinic acid in children with AD and metabolic evidence of abnormal methylation and glutathione metabolism [23]. Although we measured adaptive behavior using the Vineland Adaptive Behavior Scale (VABS) during the trial, this behavioral data has not been previously reported. We now report the change in communication, daily living, and social skills domains of the VABS associated with the three-month intervention as well as investigate whether improvement in glutathione redox status was related to any change in VABS behavior scores.

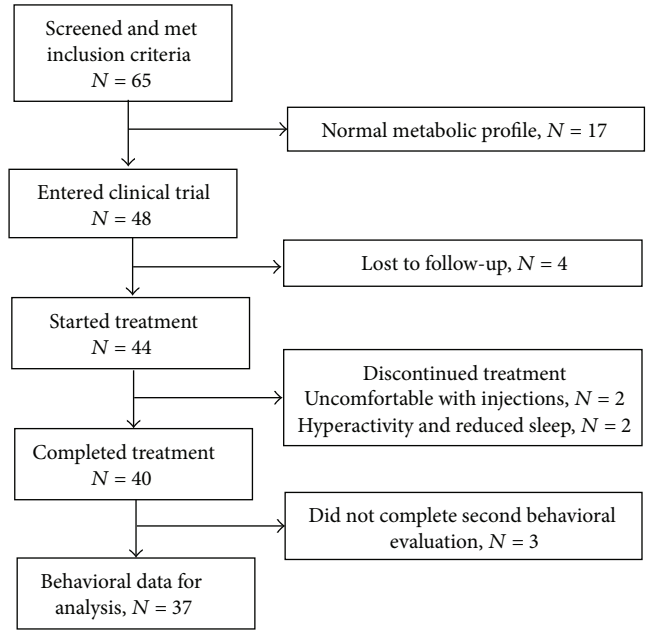

Figure 1: Flowchart of patients who met inclusion criteria for the study.

2. Methods and Materials

2.1. Participants. Forty-eight children with AD were enrolled in an open-label trial to test whether a three-month treatment of methylcobalamin (methyl B12) and folinic acid would improve glutathione synthesis as well as adaptive behavior. Inclusion criteria were a diagnosis of AD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria (299.0) and a Childhood Autism Rating Scales (CARS) score greater than 30. Exclusion criteria included Asperger's disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), genetic disorders, epilepsy, severe gastrointestinal symptoms, recent infections, and/or current use of high-dose vitamin or mineral supplements (i.e., above the recommend daily allowance). Metabolic and behavioral assessments were conducted at baseline and at the end of the 3-month intervention. A nurse contacted each family every two weeks to ensure compliance and monitor adverse effects.

Figure 1 provides a flowchart of the patients who met criteria for possible inclusion in the study. In order to determine if abnormal redox metabolism could be improved with the intervention, we selected children with abnormal glutathione redox status and methylation capacity for entry into the study. Normal glutathione redox status and methylation capacity were defined by measuring these same metabolites in typically developing control children. Sixty-five autistic children met the inclusion criteria and were initially screened for metabolic evidence of abnormal methylation capacity (SAM/SAH < 3.0) and glutathione redox metabolism (GSH/GSSG < 6.0). Of these, 48 (75%) children were found to have both abnormal methylation capacity and glutathione redox metabolism, thus meeting metabolic qualifications for

inclusion. The remaining 17 (25%) were excluded because their baseline metabolic profile was within normal range. Four children dropped out during the study and another four children were lost to follow-up. Two children dropped out of the study because the parents were uncomfortable giving the methylcobalamin injections and 2 children dropped out because of hyperactivity and reduced sleep. For the four that were lost to follow-up, every attempt was made to contact the family but they either did not response to such requests or moved out of the area and could not return for follow-up. Of the 40 remaining children who completed the study, three of the parents did not complete the second behavioral evaluation, leaving 37 children who completed both the intervention and the behavioral evaluation. Characteristics of the children that completed the study are given in Table 1. Adverse effects were minimal with occasional reports of hyperactivity, as summarized in our previous study [23] and below. All parents signed informed consent approved by the Institutional Review Board at the University of Arkansas for Medical Sciences.

2.2. Intervention. Methylcobalamin was provided as a sterile injectable liquid from Hopewell Compounding Pharmacy (Hopewell, NJ). Tuberculin syringes fitted with a 1/4 inch 31 gauge needle were prefilled with 75 μg/Kg methylcobalamin and prepared individually based on each child's weight. A demonstration and instructions for the sterile subcutaneous injection of methylcobalamin in the fatty tissue of the buttocks were given to all parents. Parents were instructed to give methylcobalamin every third day for 3 months. Folinic acid (400 μg) obtained from Custom Compounding (Little Rock, AR) was administered orally twice each day as a powder mixed with a convenient food.

The subcutaneous injectable route of administration of methylcobalamin was selected based on preliminary observations that it resulted in improvement in speech and cognition [13] and the potential for support of methionine synthase activity under conditions of oxidative stress by substituting for the oxidized inactive form of coenzyme B12 [Cob (II)]. Folinic acid (5-formyltetrahydrofolate) was selected in light of the fact that it is absorbed as the reduced metabolite is rapidly polyglutamated and is more readily available for folate-dependent reactions than the synthetic vitamin form of folic acid. In our previous study, we demonstrated that this treatment significantly improved GSH and GSSG concentrations and glutathione redox status (i.e., the GSH/GSSG ratio) [23].

2.3. Glutathione Measurement. Fasting blood samples were collected into EDTA-Vacutainer tubes and immediately chilled on ice before centrifuging at 4000 ×g for 10 minutes at 4°C. To prevent metabolite interconversion, the ice-cold samples were centrifuged within 15 minutes of the blood collection and the plasma stored at −80°C until high-pressure liquid chromatography quantification within 2 weeks after receipt. Details of the methodology for high-pressure liquid chromatography with electrochemical detection and metabolite quantitation have been previously described [24, 25].

Table 1: Characteristics of the 37 participants with autistic disorder who completed the trial.

Gender (% male)	81%
Age (mean ± standard deviation)	5.1 ± 1.4 years
Regression (% regression)	35%
Childhood Autism Rating Scale score (mean ± standard deviation)	39.2 ± 7.8

2.4. Behavioral Evaluation. The VABS (1st Edition) is a validated parent interview that provides a numerical score for adaptive functioning in the domains of communication, socialization, and daily living skills which has been shown to have good reliability and validity [26]. Nine subscales represented these three domains, specifically receptive, expressive, and writing communication, personal, domestic, and community daily living skills, and interpersonal relations, play-leisure, and coping skills. Raw scores were used in the statistical analysis while age equivalent scores are used to illustrate the magnitude of the changes in behavioral development over the treatment period and domain scaled scores are provided as a comparison of the participant sample to the general population. Higher raw, age equivalent, and scaled scores represented better performance on these measures. The VABS was administered by a trained nurse at the baseline visit and again at the end of the treatment period.

2.5. Statistics. Mixed-effects regression models were conducted via SAS version 9.3 (Cary, NC) "glmmix" procedure [27]. Raw scores were used in the statistical analysis to represent the change in behavior over the intervention period. A similar approach was used in our recent study on the effect of sapropterin treatment in children with ASD [28]. Raw scores were used due to the fact that transformation of raw scores into scaled scores is not statistically valid to follow changes in adaptive behavior especially when examining the moderating effect of a biomarker on the change in behavior and especially when there is no reference control group. For example, many children with ASD have slow or stagnant development, so their development may not change over a typical three-month interval. With an intervention, their development may approach the rate of a typically developing child. However, a child whose development changes over the three-month period at a rate equal to that of a typically developing child would have a stable unchanging scaled score. Thus, in such a case, the scaled score would appear to reflect no developmental gains over the treatment period even though the child was making developmental gains. Since the null hypothesis is that there is no change over the treatment period, an unchanging scaled score would not be statistically significant even though it would indicate developmental progress.

The first statistical model included a linear effect of time on raw scores. A random intercept was used to account for each individual's symptom level. Two-tailed alpha of 0.05 was used in all analyses. In these initial models we tested whether age, gender, and/or a history of regression influenced

Table 2: Age equivalent scores from the Vineland Adaptive Behavior Scales at baseline before and after 3-month intervention with methylcobalamin and folinic acid. The change in age equivalent scores with 95% confidence interval (CI) is also given. The overall average of all subscales is also given in the last row of the table.

Vineland subscale	Baseline age equivalent (months) (mean ± SE)	Postintervention age equivalent (months) (mean ± SE)	Change in age equivalent (months) (mean; 95% CI)
Receptive language	23.1 ± 1.8	31.4 ± 3.4	8.3 (2.9, 13.7)
Expressive language	20.6 ± 1.9	27.5 ± 2.9	6.0 (3.3, 9.4)
Written language	40.5 ± 3.8	46.7 ± 4.0	6.2 (3.4, 9.0)
Personal skills	30.5 ± 2.3	40.5 ± 3.8	10.0 (3.8, 16.2)
Domestic skills	30.3 ± 4.1	39.3 ± 5.9	9.0 (−1.4, 19.4)
Community skills	32.9 ± 2.9	36.1 ± 3.8	2.0 (−3.0, 6.9)
Interpersonal skills	18.7 ± 2.7	24.1 ± 3.9	5.4 (0.0, 10.9)
Play/leisure skills	22.0 ± 4.5	34.0 ± 4.1	12.0 (4.1, 19.6)
Coping skills	25.8 ± 2.5	34.3 ± 4.0	11.5 (4.9, 18.0)
Overall skills	26.6 ± 2.3	34.3 ± 3.6	7.7 (3.4, 12.0)

the change in the outcome measure. To illustrate the relative strength of the effect we provide the Cohen's d effect size for each significant change in outcome variables. Next we determined whether baseline and/or change in glutathione redox status (i.e., the free reduced-to-oxidized glutathione ratio) moderated changes in the outcome variables. The glutathione redox status was investigated because it significantly changed with treatment in our previous study [23]. We did not investigate the moderating effect of other metabolites as multiple statistical tests would have increased our type I error rate. We conducted two sets of analyses; one examined the moderating effect of the overall glutathione redox status and another that examined the moderating effect of the change in glutathione redox status over the treatment period. The former analysis was conducted to determine whether glutathione redox status in general was related to VABS scores, while the latter analysis was conducted to determine if the change in glutathione status was related to the change in VABS scores over the treatment period. Age, gender, and/or regression factors were included in the analyses examining the moderating effect of glutathione if they were significant in the initial model.

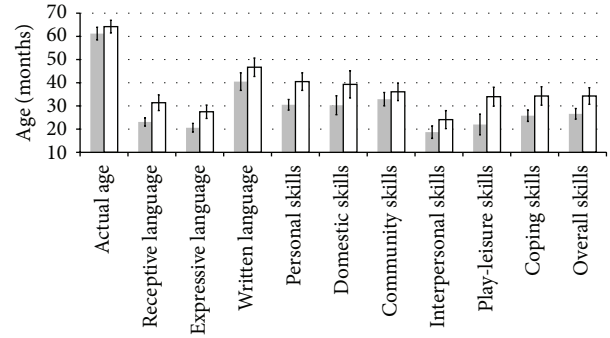

Figure 2: Histogram of actual age and age equivalents for the Vineland Adaptive Behavior Scale subscales. Error bars depict standard error.

3. Results

3.1. Behavior Change over the Intervention Period. The VABS was used to examine the impact of the intervention on measures of core behaviors associated with autism. The changes in VABS subscales with treatment were not influenced by gender, age, or history of regression, and neither gender nor history of regression was related to overall VABS subscale scores. Age was significantly related to overall raw scores for all subscales, except for interpersonal and coping skills.

Significant increases were found in all VABS subscale scores, including receptive ($F(1, 36) = 11.90, P = 0.001; d = 0.59$), expressive ($F(1, 36) = 32.80, P < 0.0001; d = 0.97$), and written ($F(1, 36) = 11.07$, $P < 0.005$; $d = 0.56$) communication skills, personal ($F(1, 36) = 14.69, P < 0.0005$; $d = 0.65$), domestic ($F(1, 36) = 4.85, P < 0.05; d = 0.37$) and community ($F(1, 36) = 9.51, P < 0.005; d = 0.52$) daily living skills, and interpersonal ($F(1, 36) = 6.45, P < 0.05; d = 0.43$), play-leisure ($F(1, 36) = 12.36, P = 0.001; d = 0.59$), and coping ($F(1, 36) = 15.68, P = 0.0005; d = 0.66$) social skills.

To illustrate the magnitude of the change in development with the intervention, Table 2 and Figure 2 present the average age equivalent for all subscales before and after the intervention. Table 2 also demonstrates the change in age equivalent with the intervention including confidence intervals. As evident from this table, many subscales, particularly those with larger effect sizes, demonstrate large gains with the three-month intervention. This is particularly true for the communication domain where skills improved between 6.0 and 8.3 months, on average, and in the social skills domain where skills improved between 5.4 and 12.0 months, on average, over a three-month period.

Baseline pretreatment scores of the individual domains and overall composite of the VABS (mean (SD): communication 65.4 (13.0); daily living skills 66.4 (13.4); social skills 67.3 (9.3); adaptive behavioral composite 66.1 (9.3)) were found to be within the range of previously published VABS scores for children with autistic disorder [15, 29]. Following intervention all individual domains and the overall

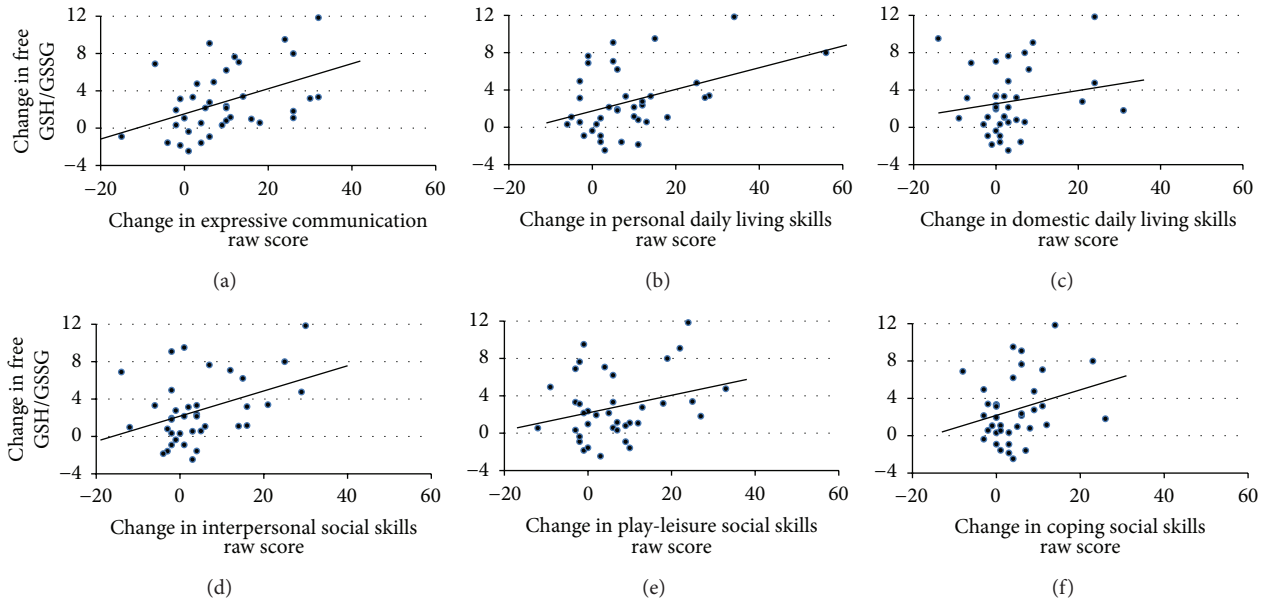

Figure 3: Significant relationships between the change in the glutathione redox status (reduced-to-oxidized glutathione ratio) and change in subscales of the Vineland Adaptive Behavior Scale (VABS) subscales. An improvement in glutathione redox status was associated with improvement in (a) expressive communication ($F(1, 33) = 9.66, P < 0.01$), (b) personal daily living skills ($F(1, 34) = 12.84, P = 0.001$), (c) domestic daily living skills ($F(1, 34) = 4.69, P < 0.05$), (d) interpersonal social skills ($F(1, 34) = 10.47, P < 0.005$), (e) play-leisure social skills ($F(1, 34) = 8.16, P < 0.01$), and (f) coping social skills ($F(1.34) = 6.09, P < 0.05$). The moderating effect of glutathione redox status on the VABS subscale is provided in the graph as a representation of the relationship between the variables. Since the linear models examining the moderating effect of glutathione redox status on the VABS subscale takes into account age, simple correlation coefficients would not be accurate for inclusion in the graphs.

composite of the VABS markedly increased (Mean (SD): communication 72.1 (15.7); daily living skills 76.0 (18.0); social skills 75.6 (16.5); adaptive behavioral composite 73.8 (17.4)).

3.2. Relation between Behavior and Glutathione Redox Status. The overall glutathione redox status was not related to VABS subscales, indicating that overall development did not appear to be related to overall glutathione redox status. In order to determine whether changes in VABS subscales were related to changes in glutathione redox status, we examined whether the glutathione redox status moderated the change in the VABS subscales. We found that glutathione redox status moderated expressive communication ($F(1, 33) = 9.66, P < 0.01$), personal ($F(1, 34) = 12.84, P = 0.001$) and domestic ($F(1, 34) = 4.69, P < 0.05$) daily living skills, and interpersonal ($F(1, 34) = 10.47, P < 0.005$), play-leisure ($F(1, 34) = 8.16, P < 0.01$), and coping ($F(1, 34) = 6.09$, $P < 0.05$) social skills such that a greater increase in the glutathione redox status (i.e., greater improvement in glutathione) was associated with a greater improvement in VABS subscale scores (see Figure 3).

3.3. Adverse Effects. The adverse effect rates are outlined in Table 3. Out of the forty-four children that started the study and were not lost to follow-up, 72% reported no adverse effects of the treatment. For the four children that dropped out of the study two children (5%) dropped out because the parents were uncomfortable giving the methylcobalamin injections and 2 children (5%) dropped out because of hyperactivity and reduced sleep. Of the 4 families who reported hyperactivity but did not drop out of the study, the hyperactivity resolved with decreasing the folinic acid dose to 400 μg per day.

Table 3: Adverse effects reported of intervention with methylcobalamin and folinic acid. All 44 children who entered the study but were not lost to follow-up were included.

Adverse effect	% (N)
Hyperactivity	14% (6)
Reduced sleep	7% (3)
Discomfort with injections	5% (2)
Insomnia	2% (1)
Impulsivity	2% (1)
Irritability	2% (1)

4. Discussion

This intervention trial was undertaken to determine whether a nutritional intervention consisting of treatment with metabolic precursors for methionine and glutathione synthesis would improve autism symptoms in children with AD. Children meeting the inclusion criteria were initially screened for metabolic evidence of abnormal methylation capacity and glutathione redox status as an indication of

potential benefit from the intervention. Our goal was to determine whether nutritional support with precursors for the abnormal metabolic pathways could result in improvement in ASD associated behavior as measured by the VABS. Overall, significant improvement was noted on all subscales of the VABS during the three-month intervention. In addition, improvement on several VABS subscales, including those related to communication and social skills, was related to the improvement in glutathione redox status. Overall, this study provides preliminary evidence that targeted nutritional support in children with AD who have metabolic abnormalities in glutathione and methylation pathways may be associated with improvements in certain behaviors associated with ASD, at least in a subset of AD children. In addition, a low rate of adverse effects with methylcobalamin and folinic acid treatment indicates that these supplements are safe and warrants further study as an intervention.

4.1. Behavioral Improvements with Intervention. A simple and safe nutritional intervention of methylcobalamin and folinic acid resulted in significant increases in VABS scores for all domains, including daily living, social, and communication skills, with an average effect size of 0.59, which is in the medium-to-large range. In fact, even the smallest effect size (domestic daily living skills, $d = 0.37$) was in the medium range and the largest effect size (expressive language skills, $d = 0.97$) was in the very large range. When considering changes in age equivalent skills over the treatment period, it was found that skills improved an average of 7.7 months over the three-month treatment period, with the lower end of the range being an average gain of 2.0 months for community daily living skills to the higher end of the range being an average gain of 12.0 months improvement for play-leisure skills. However, when we examine the overall change in scaled scores across the three-month treatment period, we find that, on average, the scaled score for the individual domains and the adaptive behavioral composite at the end of the treatment were still well below the average for typically developing children. In fact, these scaled scores were, on average, at the very lower end of normal range. Thus, although significantly improved, the behavior scores after treatment remained, on average, at the very low end of normal and for many children below the normal range. This suggests that further therapy may be required to promote continued improvement through continued nutritional treatment with metabolic precursors over a prolonged time period, the addition of intensive behavioral and educational therapy, or both.

4.2. The Relationship between Metabolic and Behavioral Changes. Change in glutathione redox status with treatment, but not baseline glutathione redox status prior to treatment, was found to be related to improvements in several VABS subscales, including all of the subscales in the social skills domain, two of three subscales in the daily living skills domain, and one of the subscales in the communication domain. Interestingly, many of the VABS subscales that were related to glutathione redox status were also subscales that demonstrated large effect sizes and larger age equivalent gains (e.g., personal daily living skills and play-leisure and coping social skills). This suggests that the marked changes in behaviors observed in these particular subscales were not simply due to a placebo-effect and may indeed be related to improvements in glutathione redox status over the three-month treatment period, although we will have to await double-blind placebo-controlled studies to validate these findings. The lack of a relationship between overall glutathione redox status and VABS scores most likely reflects the preselection of children with low glutathione redox status, thus decreasing the overall range in glutathione redox status.

In our previous study, we demonstrated that this open-label intervention significantly improved metabolites of glutathione metabolism, including total and free GSH and GSSG concentrations and the glutathione redox status (i.e., the GSH/GSSG ratio) [23]. However, despite this improvement, total and free GSH concentrations and the glutathione redox status remained significantly below those of age-matched control children. Additionally, methionine, SAM, and SAH concentrations did not significantly change with the intervention despite the fact that both methylcobalamin and folinic acid provide methyl groups for the methionine cycle. The fact that the treatment improved but did not normalize methionine, SAM and glutathione concentrations may reflect ongoing metabolic compensation for incompletely resolved oxidative stress. Thus, continued prooxidant conditions may promote glutathione synthesis as the metabolic priority at the expense of methionine transmethylation. Treatment with methylcobalamin and folinic acid appears to have rescued glutathione synthesis in this cohort of children, albeit incompletely, at the expense of transmethylation metabolism. Given the fact that some behavioral improvements were related to improvements in glutathione status, it is possible that longer-term treatment or treatments that include additional precursors or methylcobalamin and folinic acid at higher doses may result in additional behavioral improvements. For example, one recent open-label study demonstrated that high-dose folinic acid demonstrated potential efficacy in children with ASD [30] and another double-blind placebo controlled study demonstrated that N-acetylcysteine, a glutathione precursor, resulted in decreased irritability and improved social function [31]. However, neither of these aforementioned studies measured redox metabolism in order to determine whether the observed behavioral effects were related to changes in redox metabolism. Further studies will be needed to determine the optimal combination of precursors for the treatment of redox abnormalities in children with ASD.

4.3. The Use of Novel Interventions in Autism Spectrum Disorder. Our findings are consistent with smaller [31, 32] and larger [33] randomized control trials and large case series [30] demonstrating that nutritional interventions for children with ASD that target oxidative stress are associated with improvements in core ASD symptoms [30, 31], sleep and gastrointestinal symptoms [32], and hyperactivity, tantruming and parental impression of general functioning [33]. Besides the methylcobalamin and folinic acid treatment used in this study [23], the beneficial effect of nutritional treatments on

redox metabolism in children with ASD has been documented in a randomized control trial [33] and a cross-sectional study [34]. Such studies suggest that glutathione metabolism can be improved by vitamin and mineral [33] and antioxidants, coenzyme Q10 and B vitamins supplementation [34], and sapropterin treatment [28]. Thus, although there is evidence for nutritional treatments improving redox metabolism and ASD symptoms and behaviors in children with ASD, there is no specific established treatment for correcting redox abnormalities in children with ASD and the evidence for efficacy of nutritional treatments which address oxidative stress on core and associated ASD behaviors is preliminary. Clearly more studies are needed to clarify the potential beneficial effect of nutritional treatments for children with ASD.

The nutritional treatment used in this study is considered, by some, as a complementary and alternative medicine (CAM) treatment [35]. However, CAM treatments refer to a much wider variety of treatments, including nonnutritional treatments such as acupuncture and homeopathy. The prevalence of CAM in children diagnosed with a ASD in western countries is estimated to be between 32% and 87% [35] which is believed to be much higher than CAM therapies used in typically developing children [36]. Children with ASD with a greater number of medical and behavioral problems receive more CAM treatments than those with fewer medical and behavioral problems [37]. Parents believe that most CAM-associated treatments are either helpful or without effect but not harmful [35]. The main reasons parents cite for choosing to use CAM for ASD are concerns about the safety and side effects of available medications for ASD and a need to be involved in decisions involving care of their child [38]. Because the majority of CAM therapies are based on anecdotal evidence, there is a clear need for clinical trials to evaluate the efficacy of these treatments [35]. In addition, it should be noted that for ASD, of all treatments considered CAM, nutritional treatments have the most evidence for effectiveness and efficacy. Thus, it may not be proper to consider nutritional treatments, which have been used in mainstream medicine for over a century, as equivalent to CAM treatments which have undergone much fewer investigations and have less support for their use.

4.4. Limitations. The reported improvement in behavior scores by parent report should be interpreted with caution in an open-label trial because of expectation bias [38]. In addition, without a control group it is difficult to know if, and to what extent, development would have changed without treatment. As this is a group with significant delays, it is unlikely that they would have demonstrated typical gains over the three-month period but it is possible they may have shown some developmental progress. However, it is reassuring that a significant number of improvements were moderated by improvements in glutathione metabolism, suggesting that changes in metabolism were indeed related to improvements in behavior.

This study prescreened and selected a subgroup of children with ASD that demonstrated abnormal glutathione redox status and methylation capacity as a means to increase sensitivity to treatment. The broad heterogeneity of clinical and behavioral symptoms in autistic children predicts that no single treatment will benefit every autistic child. Thus, the definition and characterization of subgroups of children who respond positively or negatively to intervention will be necessary to more sensitively identify those children who are most likely to benefit from a given treatment or medication.

4.5. Conclusions. This study demonstrates that a three-month treatment with methylcobalamin and folinic acid is associated with significant improvements in behavioral symptoms associated with ASD in a group of children with AD and metabolic markers of abnormal redox and methylation metabolism. Our previous study demonstrated that this treatment also improves metabolic markers of glutathione metabolism in these same children. This provides convergence of independent measures demonstrating the beneficial effect of this simple and safe nutritional intervention. Clearly this intervention requires further study in a double-blind placebo-controlled trial to eliminate the potential bias associated with an open-label study.

Conflict of Interests

None of the authors declare a conflict of interests.

Authors' Contribution

Richard E. Frye was responsible for data analysis, interpretation, and writing of the paper. S. Jill James was the PI for this project and was responsible for the conduct of the study, interpretation of the data, and the writing of the paper. Stepan Melnyk is the laboratory director and provided HPLC expertise for metabolite analysis. George Fuchs and Tyra Reid provided clinical advice, assisted with the interpretation of data, and provided critical review of the paper. Oleksandra Pavliv provided technical assistance for the HPLC analysis. Amanda Hubanks was the study nurse who recruited patients and administered the Vineland behavior testing. David W. Gaylor provided statistical support for data analysis.

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Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials

Sun Y, Lai M S, Lu C J

CRD summary

This review assessed the effectiveness of vitamin B12 for the treatment of diabetic neuropathy. The authors concluded that vitamin B12 treatment appears to improve symptomatic relief more than electrophysiologic results. This conclusion should be viewed as tentative given the poor quality of the evidence reviewed.

Authors' objectives

To assess the effectiveness of vitamin B12 supplements for the treatment of diabetic neuropathy.

Searching

MEDLINE and the Cochrane Controlled Trials Register were searched from June 1954 to July 2004. No language restrictions were applied and the search terms were reported. In addition, the references of retrieved studies and related publications were checked. Studies that were reported as abstracts or conference presentations were excluded.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion. Uncontrolled trials and observational studies were excluded.

Specific interventions included in the review

Studies that assessed any type of vitamin B12 therapy, including coenzyme forms of vitamin B12 (methylcobalamin, cyanocobalamin, hydroxycobalamin), in either oral or injection form were eligible for inclusion. Studies involving combination therapy were also included if vitamin B12 or its coenzyme form was one of the treatment agents. The specific interventions assessed were vitamin B complex (B1, B6 and B12) as a combination agent, and methylcobalamin as a single agent. The duration of treatment ranged from 4 to 16 weeks.

Participants included in the review

Studies of participants with diabetic neuropathy were included. Diabetic neuropathy was defined as peripheral large- or small-fibre neuropathy resulting in autonomic or somatic sensory symptoms. Studies focusing on only a specific population, such as patients with uraemia, and studies in patients with other medical conditions were excluded. The primary studies were conducted in patients with type 1 and type 2 diabetes mellitus. In the included studies, the mean age of the patients was 50 to 60 years and the mean duration of diabetes mellitus, where reported, was 9 to 12 years.

Outcomes assessed in the review

Studies that reported clinical scores of somatic and autonomic symptoms or signs, vibrometer-detected thresholds of vibration perception, or electrophysiological measures such as nerve conduction velocities (NCVs) and somatosensory evoked potentials, were eligible for inclusion. The included studies used different methods to measure pain and somatosensory symptoms.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for inclusion, with any disagreements being resolved by consensus.

Assessment of study quality

The validity of the primary studies was assessed and scored according to the Jadad criteria, which address methods of randomisation, blinding, and the reporting of withdrawals and drop-outs. The maximum possible score was 5 points.

One reviewer assessed the quality of the primary studies, with a second reviewer checking for accuracy. Any disagreements were resolved by consensus.

Data extraction

One reviewer extracted the data, with a second reviewer checking for accuracy. The P-value for the differences in outcome measure scores between the treatment groups were extracted for each trial.

Methods of synthesis

How were the studies combined?

The studies were grouped according to the intervention and outcome measure and combined in a narrative.

How were differences between studies investigated?

Differences between the studies in terms of the participants and interventions were discussed in the text.

Results of the review

Seven controlled trials (n=336) were included.

Only 2 studies were judged to be of fairly good quality (Jadad score 3 out of 5). The other 5 studies were of a poor quality (Jadad score less than or equal to 2 out of 5). None of the studies involved an intention-to-treat analysis.

Pain or somatosensory symptoms (6 studies): all studies showed a statistically significant benefit compared with baseline or placebo.

Vibration perception threshold (4 studies): 3 studies showed a beneficial outcome with vitamin B12 compared with control or baseline, and one showed no improvement with methylcobalamin.

Autonomic symptoms (3 studies): all 3 studies found improvements with methylcobalamin.

Electophysiological measures (5 studies): in one trial that used a neuromotor assessment process to measure the current perception threshold, a beneficial treatment effect for vitamin B complex was observed. Of the 4 trials that included NCV testing, the only trial of vitamin B combination therapy and 2 of the 3 trials of methylcobalamin showed beneficial outcomes compared with placebo. The other study of methylcobalamin found no change.

Methylcobalamin versus conventional vitamin B12 (1 study): the study found that the outcomes were better with methylcobalamin than with conventional vitamin B12 in terms of autonomic symptoms, somatosensory symptoms and electrophysiological results.

Authors' conclusions

Among patients with diabetic neuropathy, treatment with both combination agents (vitamin B complex with cyanocobalamin) and pure methylcobalamin appeared to improve symptomatic relief more than electrophysiologic results.

CRD commentary

The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. Only two databases were searched for relevant studies, and no efforts were made to identify unpublished studies. This means that some potentially relevant studies might have been missed. Efforts were made to minimise reviewer bias and errors in the study inclusion, data extraction and quality assessment processes. Validity was assessed using established criteria, but there was no assessment of the validity of methods used to assess the outcomes.

Adequate details of the studies were presented in tabular format. The narrative synthesis of the studies was appropriate given the differences between them. However, the authors classified some studies as showing positive results when

there was an improvement from baseline, rather than an improvement in comparison with the control treatment; this can exaggerate the strength of the evidence. Some differences between the studies were discussed with respect to differences in the interventions and outcomes assessed. The authors appropriately highlighted the poor quality of the evidence base and the need for further research. Given the limited evidence from generally poor-quality, small studies, the authors' conclusions should be viewed as tentative until they are confirmed by further high-quality RCTs.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that more high-quality, double-blind RCTs are needed to confirm the clinical effectiveness of vitamin B12 and its active coenzyme. They also stated that future subgroup analyses of diabetic participants, with or without B12 deficiency, in clinical trials of vitamin therapy are important.

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Intravenous Methylcobalamin Treatment for Uremic and Diabetic Neuropathy in Chronic Hemodialysis Patients

Satoshi KUWABARA, Ryoichi NAKAZAWA*, Nakanobu AZUMA**, Mitsuru SUZUKI**, Keiko MIYAJIMA***, Toshio FUKUTAKE and Takamichi HATTORI

Object: To study the effects of the intravenous administration of methylcobalamin, an analogue of vitamin B_{12}, for uremic or uremic-diabetic polyneuropathy in patients who are receiving maintenance hemodialysis. An ultra-high dose of vitamin B_{12} has been reported to promote peripheral nerve regeneration in experimental neuropathy. Methods: Nine patients received a 500μg methylcobalamin injection 3 times a week for 6 months. The effects were evaluated using neuropathic pain grading and a nerve conduction study. Results: Serum concentrations of vitamin B_{12} were ultra-high during treatment due to the lack of urinary excretion. After 6 months of treatment, the patients' pain or paresthesia had lessened, and the ulnar motor and median sensory nerve conduction velocities showed significant improvement. There were no side effects. Conclusion: Intravenous methycobalamin treatment is a safe and potentially beneficial therapy for neuropathy in chronic hemodialysis patients.
(Internal Medicine 38: 472–475, 1999)

Key words: vitamin B_{12}, nerve regeneration

Introduction

Uremic neuropathy, recognized since the 1960s (1), now is known to be an important cause of disability in patients maintained on hemodialysis (2, 3). The clinical picture is uniform: Sensory-motor polyneuropathy begins in the distal lower extremities, and the symptoms, including dysesthesia or burning pain, ascend as the neuropathy worsens (4, 5). Renal transplantation has had striking beneficial effects (6), but the response to hemodialysis has been varied (3). Clinical signs of neuropathy tend to persist or improve very slowly, and the condition of some patients worsens in spite of an increase in the frequency of dialysis or switching to a more efficient dialyzer (3). Few therapeutic agents are available to treat polyneuropathy in chronic dialysis patients, because the mechanism of nerve damage under uremia is unknown.

Recently, Watanabe et al (7) reported that an ultra-high repeated dose of methylcobalamin, an analogue of vitamin B_{12}, promotes nerve regeneration in experimental acrylamide neuropathy. Rats treated with an ultra-high dose showed significantly faster recovery of compound muscle action potentials than the controls and the rats treated with a low dose. They speculated that the beneficial effect of an ultra-high dose of methylcobalamin is not limited to acrylamide neuropathy, and may be seen in other axonal neuropathies. Although excess vitamin B_{12} is excreted through the kidney under normal conditions, in patients with anuria the serum concentration of this vitamin is expected to be much higher than in patients without renal dysfunction and may be ultra-high after administration of the typical dose. We designed a pilot study to assess the effects of intravenous methylcobalamin treatment on polyneuropathy in chronic hemodialysis patients.

Subjects and Methods

Subjects

Of 192 patients receiving maintenance hemodialysis at a dialysis clinic, those who had polyneuropathy were singled out based on the following: a neuropathic symptom questionnaire, a neurological examination and a nerve conduction study. Seventeen had neuropathic symptoms, signs, and nerve conduction abnormalities. Of these, 7 who had severe dialysis-related amyloidosis, peripheral vascular disease, or central nervous disease were excluded. Therefore 10 patients with polyneu-

From the Department of Neurology, Chiba University School of Medicine, Chiba, the Departments of *Nephrology, **Surgery and ***Neurophysiology, Tokatsu Clinic, Matsudo

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Reprint requests should be addressed to Dr. Satoshi Kuwabara, the Department of Neurology, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670

ropathy were included in the study, 5 women and 5 men. Their ages ranged from 48 to 72 years (mean ± SD, 61.9 ± 8.8 years), and the duration of hemodialysis was 2 to 20 years (11.3 ± 8.2 years). The cause of renal failure was chronic glomerulonephritis in 5, diabetes mellitus in 4 and renal tuberculosis in 1, and neuropathy was uremic in 6, and uremic and diabetic in 4. The course of their neuropathy was slowly progressive before treatment. Informed consent for the methylcobalamin treatment, and for its assessment by nerve conduction studies, was obtained from all patients.

Methylcobalamin treatment

The patients were given 500 μg of methylcobalamin (Eisai Co. Ltd, Tokyo) i.v. three times a week for 6 months after each hemodialysis.

Clinical assessments

Clinical severity was evaluated in terms of the neurological disability score of Dyck et al (8), for grip strength, and for the grades of pain and paresthesia. Neuropathic pain or paresthesia was graded according to the modified published criteria (9): 0 = no pain/paresthesia; 1 = slight degree, not a chief complaint and analgesics not used; 2 = moderate degree, one of the chief complaints and analgesics used intermittently; 3 = severe degree, the predominant complaint, analgesics used continuously, and insomnia due to pain/paresthesia.

Electrodiagnostic studies

Nerve conduction studies were done by the conventional techniques on the median, ulnar, tibial, and sural nerves on the non-arteriovenous fistula side, at entry and 6 months after the initiation of therapy. Measurements were made of distal compound muscle action potentials (amplitude of initial negative phase), distal motor latencies, conduction velocities, and minimum F wave latencies after distal stimulation. F wave latencies were corrected for height up to 165 cm. Sensory nerve action potentials were recorded antidromically at the finger for the median and ulnar nerves and at the ankle for the sural nerve. Skin temperature was maintained above 33°C with a heat lamp.

Vitamin B_{12} assay

Vitamin B_{12} serum concentrations were measured before and 6 months after the initiation of treatment using the competitive protein binding assay, done commercially at SRL, Tokyo, Japan, (normal range, 249 to 938 pg/ml).

Results

Clinical assessments

At entry, all ten patients had sensory-dominant polyneuropathy. Muscular weakness and atrophy in the distal lower limbs were present in 3 patients. The mean neurological disability score was 38.3 (range, 8 to 66). Scores were lower in the 6 non-diabetics (range 8 to 32) than in the 4 diabetic patients (range 48 to 66). Because a 69-year-old male diabetic patient died of intracerebral hemorrhage 5 months after the start of therapy, only data from the other 9 patients were analyzed (Table 1). The neuropathic pain grading scores showed significant decreases 6 months after treatment was begun, decreasing by one grade in 4 patients. In 2 patients, the pain grade remained unchanged, but the paresthesia in the upper limbs disappeared. The neurological disability scores and grip strength values showed some improvement but the differences were not significant. There were no apparent side effects due to the methylcobalamin administration.

Nerve conduction studies

At entry, nerve conduction study results showed moderate decreases in the amplitudes of both the motor and sensory responses with mild to moderate slowing of conduction, indicative of mixed axonal and demyelinating neuropathy (Table 2). Changes in the nerve conduction parameters were analyzed in only 8 patients, because one patient refused a second examination. The ulnar motor and median sensory nerve conduction velocities were significantly increased 6 months after the initiation of treatment. Sural sensory nerve conduction velocities tended to increase. Increases in conduction velocities of more than 10% in at least 2 nerves were found in 4 patients. Most of the other parameters showed some improvement but did not reach significance.

Table 1. Changes in the Clinical Scores and Vitamin B_{12} Concentration

	before treatment	6 months later	*P* value*
Clinical assessment			
Neurological disability score	38.3 (18.1)	33.6 (18.3)	NS
Grip strength (kg)	17.6 (3.8)	19.4 (4.4)	NS
Neuropathic pain grading	1.8 (0.7)	1.4 (0.8)	0.013
Serum vitamin B_{12} concentration (pg/ml)	572 (297)	72,600 (26,900)	0.0001

*Paired t test, NS: not significant.

Table 2. Changes in Nerve Conduction Parameters

	Nerve	before treatment	6 months later	*P* value*
MOTOR STUDY				
Median	Distal latency (ms)	4.2 (1.1)	3.9 (1.1)	NS
	CV (m/s)	48.2 (5.4)	48.7 (2.4)	NS
	Amplitude (mV)	7.6 (3.0)	8.4 (3.8)	NS
	F wave latency (ms)	28.3 (7.5)	26.9 (7.3)	NS
Ulnar	Distal latency	2.8 (0.7)	2.7 (0.8)	NS
	CV	44.8 (5.1)	48.7 (5.1)	0.03
	Amplitude	7.1 (3.3)	7.9 (2.7)	NS
	F wave latency	29.8 (8.3)	26.5 (7.0)	NS
Tibial	Distal latency	4.6 (1.7)	4.1 (1.2)	NS
	CV	40.6 (4.4)	42.1 (2.6)	NS
	Amplitude	7.7 (6.2)	8.7 (6.3)	NS
	F wave latency	49.3 (13.5)	48.3 (13.2)	NS
SENSORY STUDY				
Median	CV (m/s)	40.3 (2.8)	44.2 (4.0)	0.05
	Amplitude (microV)	10.0 (6.7)	10.7 (3.7)	NS
Ulnar	CV	45.3 (2.9)	45.7 (6.0)	NS
	Amplitude	11.9 (9.1)	11.0 (9.8)	NS
Sural	CV	43.5 (3.2)	49.2 (3.9)	NS
	Amplitude	4.6 (3.8)	6.6 (4.1)	NS

Values are expressed as mean (standard deviation). *Paired t test; CV: conduction velocity, NS: not significant.

Vitamin B_{12} concentrations

At entry, the vitamin B_{12} serum concentrations ranged from 460 to 900 pg/ml (mean, 572 pg/ml), all the values being within the normal range. Methylcobalamin injection resulted in extremely high vitamin B_{12} concentrations (mean, 72,600; range, 61,000 to 91,000 pg/ml) 6 months later (Table 1).

Discussion

Our findings show that the long-term intravenous administration of methylcobalamin may have beneficial effects on uremic and diabetic neuropathies in patients receiving chronic hemodialysis. Clinical symptoms and some nerve conduction parameters showed significant improvement after 6 months of treatment. Methylcobalamin injection had no apparent adverse effects and was non-invasive when administrated through the hemodialysis line.

The mechanism that produces methylcobalamin's positive effects on nerve damage is not known. We speculate that the accumulation of exogenous methylcobalamin promotes nerve regeneration or remyelination. The results of a pathological study of uremic neuropathy (1) show that central chromatolysis of the anterior horn cells, as well as axonal degeneration of the peripheral nerve fibers, is a regular feature. Central chromatolysis is considered to represent a metabolic shift from the support of transmitter production and synaptic function to the production of materials needed for nerve regeneration (10). Biochemical findings suggest that methylcobalamin acts directly as a methyl donor in DNA metabolism and that ultra-high concentrations up-regulate gene transcription (11, 12) which may increase protein synthesis for nerve regeneration. In our series, the post-treatment serum levels of vitamin B_{12} were extremely high, more than 100-fold the pretreatment levels. Because our patients were not in a vitamin B_{12} deficiency state, the effects were not due to supplementation of vitamin B_{12}.

Another aspect of methylcobalamin's effects was the lessening of pain or paresthesia. Methylcobalamin has been reported to suppress the ectopic nerve firing in an *in vitro* experimental model: Atsuta et al (13) showed that local administration of methylcobalamin suppressed the spontaneous firing in the dog dorsal root that developed after loading hypoxia. Moreover, Kuwabara et al (14) reported that paresthesia was transiently suppressed after bolus injection of methylcobalamin in patients with various peripheral neuropathies. The significant decreases in pain grading scores in our series may be due to this suppressive effect.

Previous reports of nerve damage that responds to methylcobalamin treatment have been limited to uremic neuropathy (15, 16), although in Japan methylcobalamin is widely used to treat various peripheral neuropathies. In normal volunteers, the basal serum concentrations of vitamin B_{12} are increased after repeated intravenous injections, and vitamin B_{12} accumulates in the liver. At serum concentrations above 500 pg/ml, however, it is rapidly excreted through the kidney into the urine. The basal serum concentration therefore does not exceed 7,000 pg/ml under normal renal function, even after a daily 500 μg injection (17). Lack of urinary excretion likely

accounts for the ultra-high concentrations in uremic patients and possibly for the positive effects on neuropathy.

Because this was an open study involving a small number of patients, the placebo effects on pain or paresthesia could not be excluded; but the improvement of nerve conduction parameters is the evidence that simply placebo effects are not the primary explanation. The improvement in nerve conduction was found only in upper limb nerves in our study. This was probably due to the fact that the involvement of the upper limb nerves was less severe than the lower limb nerves (1). We suggest that the intravenous injection of methylcobalamin is a safe, non-invasive, and potentially efficacious therapy for neuropathy in patients on maintenance hemodialysis.

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Review Article

Potential Benefits of Methylcobalamin: A Review

Gupta JK* and Qureshi Shaiba Sana
Department of Pharmacology, GLA University Mathura, India

***Corresponding author:** Jeetendra Kumar Gupta, Department of Pharmacology, Institute of Pharmaceutical Research, GLA University Mathura, India

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Abstract

Methylcobalamin is an active form of vitamin B_{12} that helps in synthesis of methionine and S-adenosylmethionine. It is required for integrity of myelin, neuronal function, proper red blood cell formation and DNA synthesis. The largest group of vitamin B_{12} deficiency is found in typical vegetarians all over the world, which can be alleviated with its analogue Methylcobalamin. It is a beneficial drug to most of the common disorders like cardiovascular disorders, diabetes, anemia, hyperhomocysteinemia and degenerative disorders. Methylcobalamin helps in the synthesis of neuronal lipids, regeneration of axonal nerves and has neuroprotective activity, which promote neurons to function in proper way and thus improves Alzheimer disease, Parkinsonism, Dementia and neuropathic syndromes. It is an approved treatment for peripheral neuropathy.

Keywords: Mecobalamin; Neuropathy; Anemia; Nootropic; Dietary supplement

Abbreviations

SAMe: S-Adenosyl Methionine; ERK: Extracellular Signal-Regulated Kinases; PKB: Protein Kinase B; B-globulin: Beta Globulin; ENFD: Epidermal Nerve Fiber Density; DPN: Diabetic Peripheral Neuropathy; NSAIDs: Non Steroidal Anti Inflammatory Drugs; THF: Tetrahydrofolate; BHMT: Betaine Homocysteine Methyltransferase.

Introduction

Methylcobalamin is a potent and active form of vitamin cyanocobalamin. It plays a key role in maintaining good health. Dietary cobalamin deficiency causes many serious health problems. The commonest are blood deficiency, depression, irritability and psychosis. The long term deficiency of vitamin B_{12} substance can lead to hyperhomocysteinemia and finally cardiovascular disorder. In today's world, healthcare plays an important role in our personal lives. This merges a huge responsibility for improving and saving thousand lives on earth. Despite having incredible improvements in health since 1950, there are number of challenges which have to be solved. Each year 36 million deaths are caused by non communicable diseases such as hyperhomocysteinemia, cancer, chronic lung disease, anemia, diabetes and almost 17.5 millions died from cardiovascular disease in 2005 [1].

Folate and vitamin B_{12} are essential nutrients which are not synthesized in humans and whose deficiency is considered as heath problem worldwide such as anemia and neuronal dysfunction. Vitamin B_{12} deficiency is observed more in elderly and pregnant women. Methylcobalamin (commonly known as mecobalamin or methyl B_{12}) is an analog of vitamin B_{12} which treats or prevents the pathology arising from the deficiency of vitamin B_{12}. It contains methyl alkyl bonds and is different from cyanocobalamin because it contains cynide [2]. It has an octahedral cobalt (III) center and is produced in laboratory by reducing cyanocobalamin with sodium borohydride in alkaline solution which is followed by the addition of methyl iodide. Methylcobalamin (5 mg, 60 mg vegetarian lozenges) is active in the central nervous system outside the mitochondrion and is essential for cell growth and replication. Sometimes the liver cannot convert cyanocobalamin into adequate amount of methylcobalamin needed for proper neuronal functioning. Through enhanced methylation, it exerts its nerve cell protective effect and accelerates its growth. A lot of energy is required for cyanocobalamin to remove its cyanide and replaces it with methyl group [3]. Methylcobalamin is the only form of vitamin B_{12} that can cross the blood brain barrier without biotransformation. Its methyl group stimulates serotonin creation, a neurotransmitter which is responsible for mood enhancement and protects the brain from damage against excitotoxins. High homocysteine level is the main culprit for brain, vascular diseases, stokes risk and causes sclerosis in the arteries. Methlcobalamine converts homocysteine to methionine and reduces the potential to damage. It also forms adenosylcobalamine, the other form of vitamin B_{12} for mitochondrial energy production. Along with methylcobalamin, 5 methyltetrahydrofolate is also an important element to eliminate homocysteine. Vitamin supplements reduce the chances of building homocysteine associated with stress. Sublingual absorption of methylcobalamin has become very popular because it can be easily absorbed with better bioavailability. It also increases the available amount of SAMe (S- adenosylmethionine), which acts as a mood enhancer and works as an effective alternative to tricyclic antidepressant [4].

Therapeutic use of Methylcobalamine

Methylcobalamin is used in the treatment of diabetic neuropathy, degenerative disorders and in the preliminary treatment of amyotropic lateral sclerosis. It has been used to treat some nutrition based disease such as dementia, rheumatoid arthritis and exerts neuronal protection by promoting regeneration to injured nerves. It antagonizes the glutamate induced neurotoxicity and also manifests analgesic effects. It alleviates pain behavior in diabetic neuropathy, low back pain, neuralgia and promotes nerve conduction. It helps the body to use fats and carbohydrates for energy.

Oral administration of 500 mcg three times daily for four weeks results in improvement of peripheral neuropathy and it produces very

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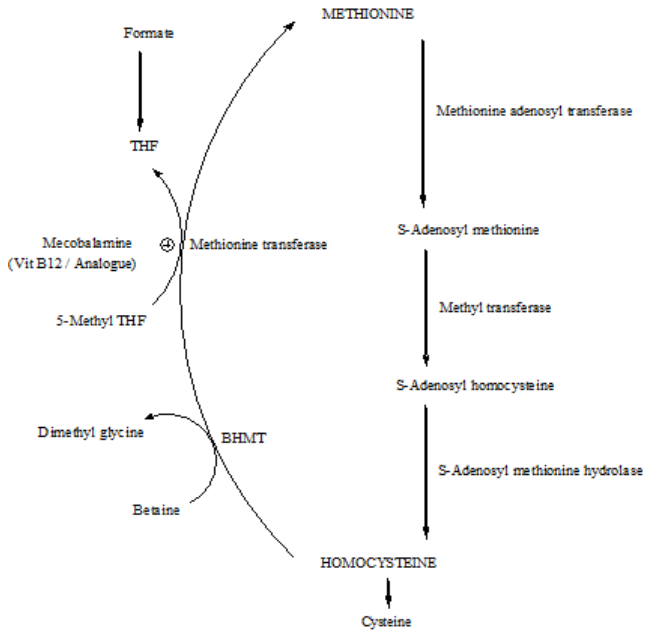

Figure 1: Mobilization of Homocysteine to Methionine by vitamin B_{12}.

significant effect after 12 weeks of treatment [5]. An improvement in vibration sense, lower motor neuron weakness and sensitivity to pain is also observed. It also improves visual function in Bell's palsy, sleep wake rhythm disorder [6].

Human urinary excretion of methylcobalamin is about one third that of a similar dose of cyanocobalamin that indicate greater tissue retention. It improves sperm count by 37.5% at a dose of 6mg per day for 16 weeks. When given at a dose of 1,500 microgram per day for 4-28 weeks results in 38% sperm concentration, sperm motility increases in 50% of cases [7-11]. Glutamate neurotoxicity was prevented by chronic exposure to methylcobalamin and SAMe. Its chronic exposure with SAMe also inhibits the neurotoxicity induced by sodium nitroprusside which is mediated by nitrous oxide. Its chronic dose also up regulate gene transcription and therefore protein synthesis. Methylcobalamin at concentration above 100nm promote neuronal survival and neurite growth, increases ERK ½ and AKT activities through methylation cycle. Continous administration of high dose of methylcobalamin results in nerve regeneration and functional recovery in rat sciatic nerve injury. Methylcobalamin (1 mg/kg intramuscular) inhibits ototoxic action of gentamycin and promote visual field defects in normal tension glaucoma. Combination of methylcobalamin, alpha lipoic acid and pregabalin improves sleep interference, nerve function and pain relief [12].

Mechanism of Action

It works by functioning in the production of a compound called myelin, which covers and protect nerve fibers [13]. Methylcobalamin rejuvenates the damaged neuron. Without enough methylcobalamin, myelin sheath does not form properly due to which nerve fibers suffers and people experience irreversible nerve damage. An intrinsic factor made in the stomach, must be present in the intestinal tract to allow its proper absorption. People lacking this factor show vitamin B_{12} deficiencies such as pernicious anemia (a slow and insidious process that can end in death. Pernicious anemia in fact means 'leading to death'). Methylcobalamin is used as a cofactor in methionine transferase enzyme, an enzyme which converts aminoacid homocysteine to methionine via folate cycle [14-16].

Pharmacokinetics

Methylcobalamin can be administered orally, parenterally and intranasal. Methylcobalamin binds with an intrinsic factor and form a complex which is absorbed in distal ileum. Its half life is 6 days. The absorption is mediated by very specific receptor mediated transport system. It is distributed to every cell of the body upon binding to Transcobalamine II, a B-globulin carrier protein and is stored in the liver in an amount of 300- 500 microgram. It is eliminated through bile. Methylcobalamin nasal sprays bioavailability is 9% [17-19].

Dose

For daily stress relief, methylcobalamin should be taken in the dose of 500 mcg per day. In the acute cases of neuropathy, dose of 1500 mcg per day can be safely taken. Dose of 1 mg per day is required to be taken for age related brain decay. Methylcobalamin can be combined with similar dose of folic acid and pyridoxine [20]. Deficiency of vitamin B_{12} is strictly seen in pure vegetarian, dose of 100 mg day can rebalance its requirement in the intestine. All human being need at least 3 mg per day of this drug for the basic nerve support. The medicine is stored in the refrigerator below 41°F (5°C) to avoid moisture. Methylcobalamin is also injected deep in to the muscles [21].

Combinations / Interactions

Fixed dose combination of sustained release pregabalin and methylcobalamin reduces neuropathic pain. Treatment with lipoic acid – methylcobalamin for 2-4 weeks is associated with better outcome in nerve conduction velocity and neuropathic symptoms. Oral combinations of methylcobalamin, L-methylfolate and Pyridoxal-5 phosphate improves Epidermal Nerve Fiber Density (ENFD) with Diabetic Peripheral Neuropathy (DPN). Medicines such as Antibiotics (penicillin, cefalexin, ciprofloxacin), metformin, nitrous oxide, colchicines, NSAIDs (Ibuprofen, Para aminosalicyclic acid, sulphasalazine) decrease the absorption and induce reversible mal-absorption of methylcobalamin by altering the function of ilea mucosa. Some drugs like nitrates (nitroglycerin), fluorouracil interacts with methylcobalamin and their side effects are increased [22]. Chloramphenicol antagonizes the hematopoietic action of this drug. Administration of methylcobalamin during pregnancy and breast feeding is dangerous because it can cross maternal-fetal barriers and also gets excreted in milk. Barbiturates (phenobarbitol), primidone, pyrimethamine, valproic acid, hydantoins should not be taken along with methylcobalamin because their effectiveness is inhibited. Aminoglycosides, proton pump inhibitors, anti hyperglycemic medications (metformin), anticonvulsants interfere with methylcobalamin absorption and function. Consumption of ethanol along with methylcobalamin therapy counteracts its action [13,23-25].

Adverse Effects

At a very high dose, methylcobalamin causes blood clots, diarrhea, paresthesia, rhinitis, ataxia, pruritis and allergic reactions.

People with polycythemia should consult with a physician before taking this therapy [26-29]. This drug can be applied as a topical paste on the skin without any adverse reaction. Sometimes intravenous injection of this drug leads to hypersensitivity reactions and end up to anaphylactic shock. In some cases, hypokalamia and thrombocytosis has occurred in the patient while treating megaloblastic anemia with methylcobalamin [30-37].

Conclusion

Methylcobalamin aids in growth of healthy blood cells, nerve cells in the body. It is a best treatment as well as dietary supplement for the people who cannot absorb vitamin B_{12} and / or suffers from its deficiencies. Monotherapy of methylcobalamin improves plasma / serum homocysteine level and improve the neuropathic symptoms also [28-37]. Combination therapy with other vitamin B complexes seems to be more effective. Hence methylcobalamin may be considered as one of the promising dietary supplement and medicine having a number of potential benefits [5,38-41].

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Review Article

Methylcobalamin: A Potential Vitamin of Pain Killer

Ming Zhang, Wenjuan Han, Sanjue Hu, and Hui Xu

Institute of Neurosciences, The Fourth Military Medical University, Xi'an 710032, China

Correspondence should be addressed to Hui Xu; xubz@fmmu.edu.cn

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Methylcobalamin (MeCbl), the activated form of vitamin B12, has been used to treat some nutritional diseases and other diseases in clinic, such as Alzheimer's disease and rheumatoid arthritis. As an auxiliary agent, it exerts neuronal protection by promoting regeneration of injured nerves and antagonizing glutamate-induced neurotoxicity. Recently several lines of evidence demonstrated that MeCbl may have potential analgesic effects in experimental and clinical studies. For example, MeCbl alleviated pain behaviors in diabetic neuropathy, low back pain and neuralgia. MeCbl improved nerve conduction, promoted the regeneration of injured nerves, and inhibited ectopic spontaneous discharges of injured primary sensory neurons. This review aims to summarize the analgesic effect and mechanisms of MeCbl at the present.

1. Introduction

Vitamin B12 had been usually treated as sport nutrition, and used to keep old people from getting anemic in past years. Vitamin B12 was regarded as painkilling vitamin in some countries from 1950. Recently studies have shown that vitamin B12 played a key role in the normal functioning of the brain and nervous system and the formation of blood. Vitamin B12 is normally involved in several metabolisms such as DNA synthesis and regulation, fatty acid synthesis, and energy production. Vitamin B12 has some analogs including cyanocobalamin (CNCbl), methylcobalamin (MeCbl), hydroxocobalamin (OHCbl), and adenosylcobalamin (AdoCbl). In mammalian cells, CNCbl and OHCbl are inactive forms and AdoCbl acts as a coenzyme of methylmalonyl Co-A mutase in mitochondria. However, vitamin B12 was not used directly in human body, and it should be translated into activating forms such as MeCbl or AdoCbl. MeCbl differs from vitamin B12 in that the cyanide is replaced by a methyl group (Figure 1) [1]. It is a coenzyme of methionine synthase, which is required for the formation of methionine from homocysteine in the methylation cycle which involves methylation of DNA or proteins [2–5]. Compared with other analogs, MeCbl is the most effective one in being uptaken by subcellular organelles of neurons. Therefore, MeCbl may provide better treatments for nervous disorders through effective systemic or local delivery.

As an auxiliary agent, MeCbl has been always used to treat many diseases, such as B12 deficiency and Alzheimer's disease syndromes [6, 7]. L-methylfolate, MeCbl, and N-acetylcysteine improved memory, emotional functions, and communication with other people among Alzheimer's patients [7, 8]. MeCbl also has neuronal protection including promoting injured nerve and axonal regeneration [9, 10] and confronting against glutamate-induced neurotoxicity [9, 11]. In addition, MeCbl improved nerve conduction in either patients of diabetic neuropathy [12–14] or streptozotocin-diabetic rats [15] and experimental acrylamide neuropathy [16]. MeCbl also improved visual function [17], rheumatoid arthritis [18], Bell's palsy, and sleep-wake rhythm disorder [19, 20]. Recently, MeCbl has been demonstrated to have potential analgesic effects on neuropathic pain in experimental and clinical studies.

2. The Analgesic Effect of MeCbl

MeCbl is one active form of vitamin B12 which can directly participate in homocysteine metabolism. More and more researches showed that MeCbl has beneficial effects on clinical and experimental peripheral neuropathy.

Table 1: The analgesic effect of MeCbl or combined use with other drugs on patients with diabetic neuropathic pain.

Effects of MeCbl	Indices	Measures of intervention	Reference
Alleviation of neuropathic pain symptoms; improved nerve conduction velocity	Pain scale scores of patients; measure of nerve conduction velocity	Oral administration of MeCbl for 3 months	Devathasan et al. [12]
Improved nerve conduction velocity	Measure of nerve conduction velocity	Intravenous administration of MeCbl	Ishihara et al. [14]
Improved the symptoms of paresthesia, burning pains, and heaviness; no effect on nerve conduction velocity	Pain symptoms; measure of nerve conduction velocity	Repeated intrathecal injection of MeCbl at a high dose of 2.5 mg/10 mL	Ide et al. [21]
Relieved spontaneous pain by 73%	Likert-type pain intensity scale; Patients' Global Impression of Change (PGIC) scale	Intramuscular injection of MeCbl for four weeks followed by oral administration of MeCbl for additional eight weeks	Li [22]
Relieved pain and paresthesia; improved motor and sensory nerve conduction velocity	Neurolgical disability score for the grades of pain and paresthesia	Intravenous injection of MeCbl for 6 weeks	Kuwabara et al. [13]
Reduced pain scores and good tolerance	Visual analog scale and chemical safety	Oral administration of immediate-release methylcobalamin and sustained-release pregabalin for 2 weeks.	Dongre and Swami [23]

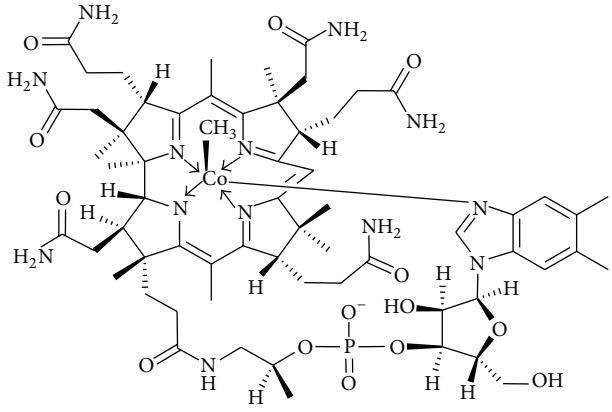

Figure 1: The chemical structure of MeCbl.

2.1. Diabetic Peripheral Neuropathic Pain. Clinical symptoms in legs, such as paresthesia, burning pains, and spontaneous pain, were ameliorated by MeCbl [21, 22] (Table 1). The effects of single use of MeCbl or combined use with other drugs were reviewed in diabetic neuropathy pain [12, 23] (Table 1). Clinical evidence proved that MeCbl had the capacity to inhibit the neuropathic pain associated with diabetic neuropathy.

The intensity of the pain is variable and may be described as a hot, burning, cold, aching, or itching sensation with, at times, increased skin sensitivity. In clinics, it is still a challenge to treat diabetic neuropathic pain. Carbamazepine and dolantin were not able to relieve these symptoms. Similarly, therapeutic effects of aldose reductase inhibitors and nimodipine were not encouraging in clinic as much as basic studies showed. Fortunately, MeCbl may bring a glimmer of hope to treat diabetic neuropathic pain.

2.2. Low Back Pain. Between 70 and 80% adults have experienced low back pain at some times in their life [24]. Back pain is one of the most common health complaints. But the causes are extensive, cancer, infection, inflammatory disorders, structural disorders of the spine itself, and disk herniation, are somewhat more common, and together account for back pain. It is supposed that the MeCbl is becoming a decent choice for the therapy to the chronic low back pain. Neurogenic claudication distance was improved significantly after the application of MeCbl [25] (Table 2). However Waikakul's research demonstrated that MeCbl was not good for pain on lumbar spinal stenosis [25]. In a trial, the analgesic effect of MeCbl has been investigated in nonspecific low back pain patients with intramuscular injection [26] (Table 2). The inconsistent effect of MeCbl might be due to different causes of lumbar spinal stenosis and nonspecific low back pain. Further studies are needed to determine the effect of MeCbl on low back pain.

2.3. Neck Pain. Chronic neck pain is becoming a common problem in the adult population, for the prevalence of 30%–50% in 12 months [27, 28]. It was shown that spontaneous pain, allodynia, and paresthesia of patients with neck pain were improved significantly in the MeCbl group, and with the increase of treatment time of MeCbl, the analgesic effect was more obvious [29] (Table 2).

2.4. Neuralgia

2.4.1. Subacute Herpetic Neuralgia. The treatment of MeCbl significantly reduced continuous pain, paroxysmal pain, and allodynia in the subacute herpetic neuralgia (SHN) patients [30] (Table 3). Thus, MeCbl may be an alternative candidate for treating SHN.

Table 2: The analgesic effects of MeCbl on low back pain and neck pain in clinical trials.

Effects of MeCbl	Indices	Measures of intervention	Reference
Relieved spontaneous pain, allodynia, and paresthesia.	Pain symptoms of patients with neck pain	Oral administration of MeCbl for 4 weeks	Hanai et al. [29]
Amelioration of neurogenic claudication distance; no effect on pain improvement and neurological signs	Pain symptoms; measure the neurogenic claudication distance of patients with degenerative lumbar spinal stenosis	Oral administration of MeCbl as an adjuvant medication for 6 months	W. Waikakul and S. Waikakul [25]
Reduced pain	Oswestry disability index questionnaire (ODI) and visual analogue scale (VAS) pain score of patients with nonspecific low back pain	Intramuscular injection of MeCbl for 2 weeks	Chiu et al. [26]

Table 3: The analgesic effect of MeCbl or combined with other agents on neuralgia.

Effects of MeCbl	Indices	Measures of intervention	Reference
Reduced or eliminated pain symptoms	Pain scales in patients with trigeminal neuralgia	Intravenous injection of MeCbl at a single dose of 0.5 mg	Teramoto [32]
Relieved overall pain, continuous spontaneous pain, paroxysmal pain, and allodynia	Likert-type pain intensity scale; Patients' Global Impression of Change (PGIC) scale	Local subcutaneous injection of MeCbl for 4 weeks	Xu et al. [30]
Lowered pain intensities; improved pain relief; reduced pain interference with quality of life	Numerical pain scale and brief pain inventory of glossopharyngeal neuralgia	Oral administration of gabapentin, tramadol, and MeCbl (0.5 mg)	Singh et al. [31]

2.4.2. Glossopharyngeal Neuralgia. Glossopharyngeal neuralgia (GPN) is a common facial neuralgia in the pain clinics. It was reported that the numerical pain scales were decreased substantially with the treatment of MeCbl combined with gabapentin and tramadol in GPN patients [31] (Table 3). And degree of interference in quality of life including mood, interpersonal relationship, and emotion was improved earlier [31].

2.4.3. Trigeminal Neuralgia. The pain of trigeminal neuralgia (TN) can be described as agonizing, paroxysmal and lancinating which may be activated by small activities such as chewing, speaking, and swallowing. A clinical trial proved that the pain of TN patients was alleviated greatly in the MeCbl group, and no recurrence of TN in pain symptoms was closed to 64% [32] (Table 3).

2.5. Neuropathic Pain of Animal Models. The coapplication of MeCbl and pioglitazone dramatically decreased allodynia and hyperalgesia in diabetic rats [33]. And the combined application of MeCbl and vitamin E alleviated thermal hyperalgesia in sciatic nerve crush injured rats [34]. Our recent work observed that tactile allodynia was markedly alleviated following a chronic treatment of MeCbl injection in chronic compression of dorsal root ganglion (CCD) rats (Figure 2).

3. Mechanisms Underlying the Analgesic of MeCbl

For many years, the B12 group of vitamins had been used to treat pain. In some countries, vitamin B12 was categorised as an analgesic drug. It was suggested that vitamin B12 may increase availability and effectiveness of noradrenaline and 5-hydroxytryptamine in the descending inhibitory nociceptive system [35]. MeCbl exerted therapeutic effects on neuropathic pain in diabetics, possibly through its neurosynthesis and neuroprotective actions [13, 36]. But the analgesic mechanisms of MeCbl remained elusive till now.

3.1. Improving Nerve Conduction Velocity. Previous studies showed that high doses of MeCbl improved nerve conduction in either patients with diabetic neuropathy [12–14], streptozotocin-diabetic rats [15], or experimental acrylamide neuropathy [16]. Morphological and histological evidence confirmed that a long-term administration of MeCbl promoted the synthesis and regeneration of myelin [37]. These morphological and histological recoveries of myelin may result in improving nerve conduction velocity and neuronal function in peripheral neuropathy.

3.2. Promoting the Regeneration of Injured Nerves. MeCbl advanced the incorporation of radioactive leucine into the protein fraction of the crushed sciatic nerve in vivo. As a result, the activity abilities of injured nerve were recovered [38]. In this study, the most terminals were degenerated in the mutant mouse, but the sprouts were more frequently observed in the MeCbl treatment group [39]. MeCbl had the ability to promote the injured nerves regeneration. In the experimental acrylamide neuropathy and sciatic nerve injury models, the number of regenerations of motor fibers showed significant increase with high-dose methylcobalamin [16]. And the combined use of L-methylfolate, MeCbl, and pyridoxal 5′-phosphate improved the calf muscle surface neural density [40].

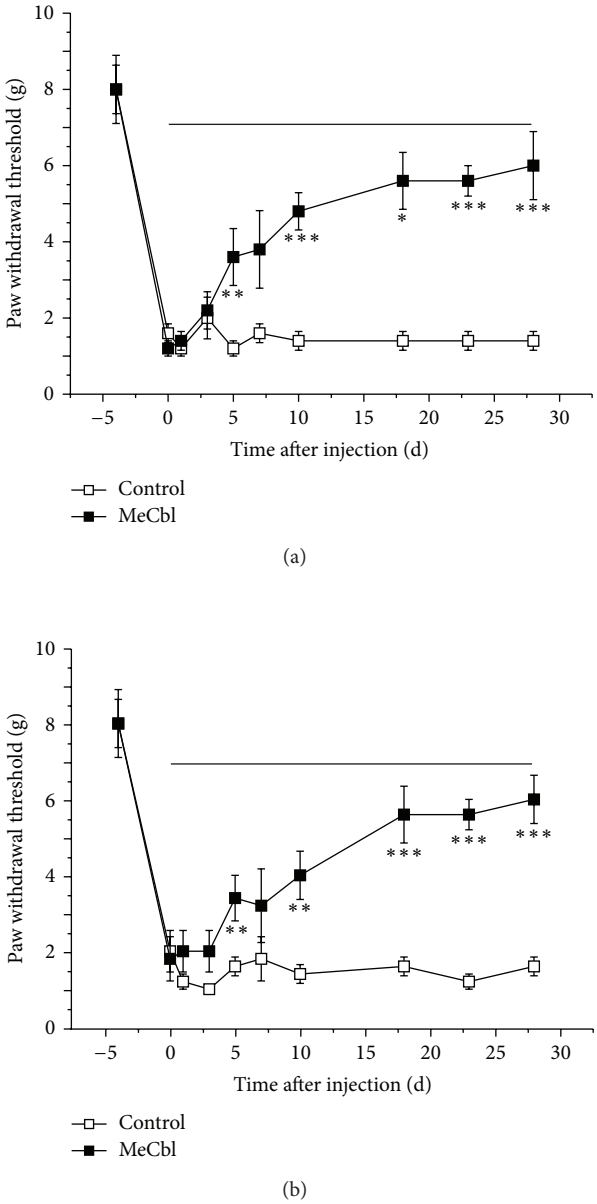

Figure 2: An anti-allodynic effect of MeCbl. MeCbl was successively received by intraperitoneal injections from the 3rd postoperative day (line segment). Bilateral paw withdrawal thresholds to von Frey filaments were decreased following a long-term application of MeCbl. (a) Ipsilateral side and (b) contralateral side. ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, multivariate analysis of variance).

3.3. Inhibiting Ectopic Spontaneous Discharge. Ectopic spontaneous discharges are likely to initiate spontaneous pain, hyperalgesia, and allodynia [41–45]. It was reported that MeCbl suppressed the ectopic firing induced by chemical materials in the dog dorsal root [46]. Our recent work demonstrated that MeCbl markedly inhibited the ectopic spontaneous discharges of dorsal root ganglion neurons in CCD rats (Figure 3). Our results suggested that MeCbl exhibited its anti-allodynic effect by inhibiting peripheral pain signals.

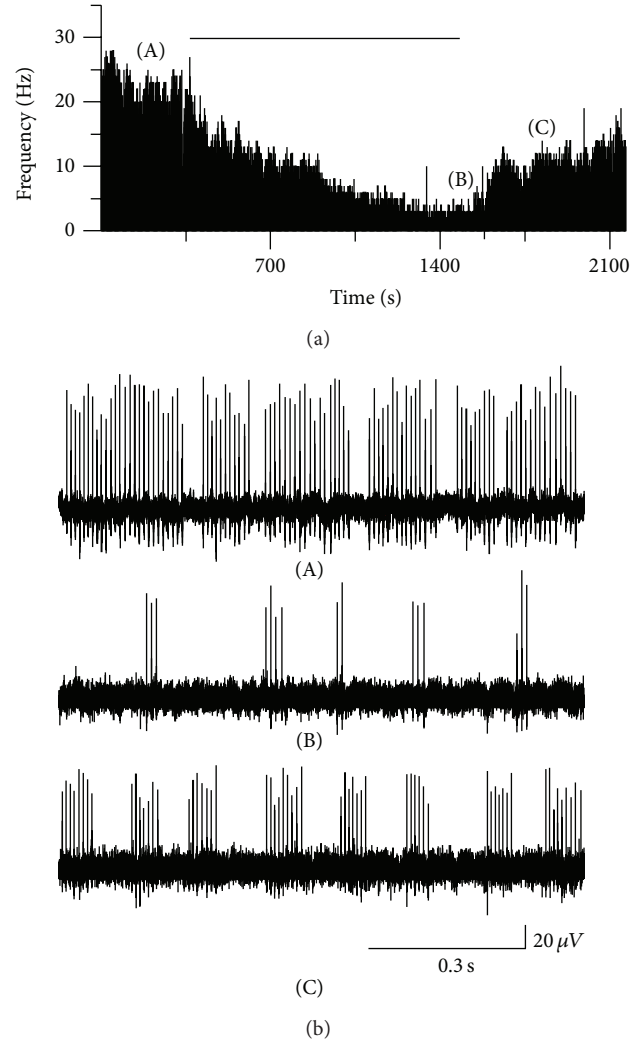

Figure 3: Inhibitory effect of MeCbl on ectopic spontaneous discharges of dorsal root. (a) Time histogram showing that local application of the MeCbl (300 μmol/L) decreased the basal firing rate of dorsal roots. (b) Three traces in right panel show firing patterns before (A), during (B), and wash out (C) the application of MeCbl.

4. Conclusions

MeCbl or its combined use with other agents has the potential analgesic effect in specific patients and animal models, for example, nonspecific low back pain; neck pain; diabetic neuropathic pain, subacute herpetic neuralgia, glossopharyngeal neuralgia, and trigeminal neuralgia. However, its mechanisms underlying the analgesic effect were poorly understood. On the basis of recent work, the possible mechanisms can be considered as follows. (1) MeCbl improved nerve conduction velocity; (2) MeCbl promoted injured nerve regeneration, recovering the neuromuscular functions in peripheral hyperalgesia and allodynia; and (3) MeCbl inhibited the ectopic spontaneous discharges from peripheral primary sensory neurons in neuropathic pain states. As a vitamin, MeCbl may be a potential candidate for treating peripheral neuropathy with good safety.

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Descriptive Information

Brief Title ICMJE	A Study in Patients With Amyotrophic Lateral Sclerosis (ALS) ClinicalTrials.gov Identifier NCT00444613. **Sponsor: Esai Co., Ltd.**
Official Title ICMJE	A Phase II/III Study in Patients With Amyotrophic Lateral Sclerosis (ALS)
Brief Summary	The purpose of this study is to investigate the efficacy and confirm the safety of E0302 in patients with Amyotrophic Lateral Sclerosis (ALS) by assessing changes in scores of survival rate and functional rating scale.
Detailed Description	*Not Provided*
Study Type ICMJE	Interventional
Study Phase	Phase 2 Phase 3
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment
Condition ICMJE	Amyotrophic Lateral Sclerosis (ALS)
Intervention ICMJE	• Drug: E0302 (mecobalamin) Intramuscular injection, mecobalamin 25 mg twice a week for 3.5 years. Other Name: mecobalamin • Drug: E0302 (mecobalamin) Intramuscular injection, mecobalamin 50 mg twice a week for 3.5 years. Other Name: mecobalamin • Drug: Placebo Intramuscular injection, placebo twice a week for 3.5 years.
Study Arms	• Experimental: E0302 25 mg Intervention: Drug: E0302 (mecobalamin) • Experimental: E0302 50 mg Intervention: Drug: E0302 (mecobalamin) • Placebo Comparator: 3 Intervention: Drug: Placebo
Publications *	Ikeda K, Iwasaki Y, Kaji R. Neuroprotective effect of ultra-high dose methylcobalamin in wobbler mouse model of amyotrophic lateral sclerosis. J Neurol Sci. 2015 Jul 15;354(1-2):70-4. doi: 10.1016/j.jns.2015.04.052. Epub 2015 May 8.

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Nephrology Dialysis Transplantation

Preliminary Communication

Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation

Katsushi Koyama, Takeshi Usami, Oki Takeuchi, Kunio Morozumi and Genjiro Kimura

Department of Internal Medicine and Pathophysiology, Nagoya City University Medical School, Mizuho-ku, Nagoya 467-8601, Japan

Abstract

Background. Hyperhomocysteinaemia, which is considered to be induced by impairment of the remethylation pathway in patients with chronic renal failure (CRF), cannot be cured solely by folic acid therapy. In the present study, we investigated the additional benefit of administration of methylcobalamin, which is a co-enzyme in the remethylation pathway, on lowering total homocysteine (tHcy) plasma concentrations in haemodialysis (HD) patients receiving high-dose folic acid supplementation.

Methods. In order to assess the efficacy on lowering plasma tHcy levels (fasting concentration), 21 HD patients, were randomly assigned and provided folic acid supplementation: 15 mg/day orally (group I, $n=7$); methylcobalamin 500 mg intravenously after each HD, in addition to folic acid (group II, $n=7$); or vitamin B_6 (B_6), 60 mg/day orally, in addition to folic acid and methylcobalamin (group III, $n=7$). All patients were treated for 3 weeks. A methionine-loading test was conducted before and after supplementation. The following measurements were also made before and after supplementation for each group: serum folic acid, B_6, and vitamin B_{12} (B_{12}) concentrations (including measurement of proportion of methylcobalamin fraction). Twelve HD patients receiving methylcobalamin alone served as the HD control group and seven healthy volunteers served as the normal control group for this study.

Results. In our randomized HD patients the proportions of methylcobalamin fraction ($48.3 \pm 7.5\%$) and plasma vitamin B_6 concentration (2.9 ± 1.1 ng/ml) were significantly lower than in the normal controls (methylcobalamin $58.7 \pm 2.2\%$, $P<0.01$; B_6 20.1 ± 10.8 ng/ml, $P<0.01$), while folic acid and vitamin B_{12} were not significantly different from the normal controls. Mean percentage reduction in fasting tHcy was $17.3 \pm 8.4\%$ in group I, $57.4 \pm 13.3\%$ in group II, $59.9 \pm 5.6\%$ in group III, and $18.7 \pm 7.5\%$ in HD controls. The power of the test to detect a reduction of tHcy level was 99.6% in group II and 99.9% in group III when type I error level was set at 0.05. Groups II and III had normal results for the methionine-loading test after treatment. Treatment resulted in normalization of fasting tHcy levels (<12 ng/ml) in all 14 patients treated by the combined administration of methylcobalamin and supplementation of folic acid regardless of whether there was supplementation of vitamin B_6.

Conclusion. The benefit of methylcobalamin administration on lowering plasma tHcy levels in HD patients was remarkable. Our study suggested that both supplementations of high-dose folic acid and methylcobalamin are required for the remethylation pathway to regain its normal activity. This method could be a therapeutic strategy to combat the risk associated with atherosclerosis and cardiovascular disease in patients with chronic renal failure.

Keywords: chronic renal failure; folic acid; haemodialysis; homocysteine; methylcobalamin; vitamin B_{12}

Introduction

Hyperhomocysteinaemia was recently recognized as a risk factor for the development of atherosclerotic vascular diseases [1]. In patients with chronic renal disease, plasma total homocysteine (tHcy) levels are elevated, in an inverse relationship with the reduction in renal function [2]. Most reports showed that at least 80% of dialysis patients have markedly increased levels of tHcy [2].

Homocysteine is formed as an intermediate metabolic product of methionine at the junction

Correspondence and offprint requests to: Katsushi Koyama, MD, Department of Internal Medicine and Pathophysiology, Nagoya City University Medical School, Mizuho-ku, Nagoya 467-8601, Japan. Email: kk0114@med.nagoya-cu.ac.jp

of two metabolic pathways: remethylation and trans-sulfuration [3]. Homocysteine can either be remethylated to methionine or be trans-sulfurated to cysteine. In remethylation, homocysteine receives a methyl group from 5-methyltetrahydrofolate or from betaine. Vitamin B_{12} is a necessary cofactor in the folate-dependant remethylation. Trans-sulfuration requires vitamin B_6 as the cofactor. Impairment of remethylation is strongly implicated as the cause of hyperhomocysteinaemia in uraemic patients [4].

Folic acid is vital in humans for several metabolic reactions, including the remethylation pathway. However, clinical studies have shown that hyperhomocysteinaemia in uraemic patients cannot be cured solely by folic acid therapy [5]. Vitamin B_{12} (cyanocobalamin) supplementation alone and a combined supplementation of vitamin B_{12} (cyanocobalamin) with folic acid were reported to be effective in reducing homocysteine levels, but full normalization of hyperhomocysteinamia was not achieved [6–8]. Hence, other strategies are needed to combat these risks associated with atherosclerosis and cardiovascular disease in patients with chronic renal failure (CRF).

We reported previously a decreased proportion of methylcobalamin fractionin the total serum vitamin B_{12} concentration in patients with CRF [9]. Methylcobalamin is the co-enzymatic form of the vitamin B_{12} analogues, which is required in the remethylation pathway. Therefore, we were encouraged to investigate the potential involvement of methylcobalamin in hyperhomocysteinaemia in patients with CRF. In this study, we specifically investigated the additional benefit of administration of methylcobalamin on lowering the tHcy plasma levels in haemodialysis (HD) patients with supplementation of folic acid. We also implemented a methionine-loading test in order to assess a whole body homocysteine handling.

Subjects and methods

Participants were CRF patients who started HD therapy at the Kidney Center in Nagoya City University Hospital ($n=21$). Exclusion criteria were as follows: (i) presence of anaemia, haematocrit $<25\%$, (ii) known history of diabetes mellitus, (iii) patients with homocystinuria, (iv) patients with liver dysfunction, (v) smokers, (vi) serious systemic disease, and (vii) specific indication for or contraindication to a study drug or study procedure. (Any additional vitamin other than vitamin D3 was not given during the study period.) The majority of the participants were on regular therapy with recombinant human erythropoietin and iron. Enrolment of the study participants was from October 1999 until May 2000 and from January 2001 until April 2001. Participants were randomly assigned to receive supplementation of 15 mg/day of folic acid orally (group I, $n=7$); 500 μg of methylcobalamin (Methycobal, Eisai Co., Ltd, Tokyo) intravenously after each HD plus 15 mg/day of folic acid orally (group II, $n=7$); or, 60 mg/day of vitamin B_6 plus 15 mg/day of folic acid orally and 50 g methylcobalamin intravenously after each HD (group III, $n=7$). All patients were treated for 3 weeks.

Twelve HD patients served as volunteers (HD control group) to receive methylcobalamin treatment without supplementation of folic acid. Exclusion criteria were the same as those for our randomized study. These patients were given 500 mg methylcobalamin intravenously after HD for 3 weeks.

All patients were dialysed three times a week for a total of 12 h weekly, using bicarbonate-based dialysate and polysulfone dialysers. We maintained K_t/V above 1.2 throughout the study period. Seven healthy volunteers (four men, three women) also served as the normal control group. Both the HD control group and the normal control group were forbidden to take any kind of vitamin supplement. The study protocol was approved by the institutional review board of Nagoya City University Medical School, and written informed consent was obtained from each patient and volunteer.

Measurement of total serum concentrations of folic acid, vitamin B_6, vitamin B_{12}, and proportion of methylcobalamin fraction of serum total vitamin B_{12}.

Serum folic acid, vitamin B_6, and vitamin B_{12} concentrations were measured before and after supplementation in all the subjects. Blood was sampled in the early morning at fasting condition; in the HD patients, it was drawn on a day when HD was scheduled. The proportion of methylcobalamin fraction of serum total vitamin B_{12} concentrations was measured before and after supplementation in the patients who participated in our randomized study. Determination of serum vitamin B_6 concentration was performed by a high-performance liquid chromatography equipped with a fluorescence detector with normal range of 4.0–19.0 ng/ml. Serum concentrations of vitamin B_{12} were measured by competitive assay, while those of folic acid were by competitive immunoassay using the automated chemiluminescence systems. The normal ranges for serum concentration were 2.4–9.8 ng/ml for folic acid and 233–914 pg/ml for vitamin B_{12}.

To obtain the methylcobalamin fraction, venous blood was drawn into foil-wrapped syringes before HD, and serum was separated in a dark room under red photographic light to avoid the photolysis of vitamin B_{12} analogues including cyanocobalamin, hydroxycobalamin, deoxyadenosycobalamin, and methycobalamin. The methylcobalamin fraction, separated using high-performance liquid chromatography, was determined by bioautographic analysis of the chromatogram using *Lactobacillus leichmannii* (ATCC10586) as the test organism [10,11].

Measurement of plasma tHcy concentration at fasting and methionine-loading test

The measurement of plasma tHcy concentration was conducted by a rapid, isocratic high-performance liquid chromatography assay [12]. The normal range for plasma tHcy level at fasting was 3.0–14.0 nmol/ml.

The measurement of plasma tHcy concentration at fasting and the methionine-loading test were conducted before and after supplementation in all the patients who participated in our randomized study and in 12 HD controls. All of the patients and control subjects received 0.05 g of methionine per kg of body weight after fasting for 12 h. The oral methionine challenge (100 mg/kg) is useful for diagnosis of cystathione-beta-synthase deficiency

or MTHFR reductase deficiency [13]. Because HD patients have shown an exaggerated increase in plasma tHcy level after the methionine loading [14], we considered that a half dose of methionine (50 mg/kg) loading was sufficient to assess the metabolic pathway of homocystenine in HD patients as reported by Hirose *et al.* [15]. In HD patients, methionine was loaded on a day when HD was not performed. As methionine has a slightly unpleasant smell, we administered it orally with a sugar-based non-protein containing flavour. The plasma tHcy concentrations were measured prior to and 2 and 4 h after methionine administration.

Statistical analysis

All numeric data, including the primary end points of plasma tHcy concentration were expressed as the mean $\pm$ SD, and the level $P < 0.05$ was considered to be statistically significant. Mean values with 95% confidence intervals (CI) are also expressed for the primary end points of post-treatment plasma tHcy levels. Secondary end points were serum concentrations of vitamins: folic acid, vitamin B_6, vitamin B_{12}, and the proportion of methylcobalamin fraction of serum total vitamin B_{12}.

For the baseline values of plasma tHcy concentrations at fasting, serum concentrations of folate, vitamin B_{12} and vitamin B_6, age, HD duration, sex, haematocrit, serum urea nitrogen, serum creatinine, β_2-microglobulin, and albumin concentrations, a one-way ANOVA of the grouping variable was performed to exclude potential differences between HD patients groups including the three randomized HD groups and HD controls. The proportion of methylcobalamin fraction in total serum vitamin B_{12} concentration was analysed by a one-way ANOVA between the randomized HD groups. Differences in gender were analysed by χ^2-test. Treatment effects on percentage changes in fasting plasma tHcy levels were presented as [(average pretreatment level−average post-treatment level)/average pretreatment level]$\times$100. The difference in the change in fasting plasma tHcy levels between the treatment groups was evaluated by a two-way repeated-measures ANOVA (type I error level of statistical analysis was set at $\alpha = 0.05$). Effects of vitamin supplementation on serum vitamin concentrations in each group were analysed by the Student's *t*-test.

The results from the methionine-loading test were analysed by a two-way repeated-measures ANOVA to assess the effect of each vitamin supplementation regimen (folic acid alone, folic acid with methylcobalamin, folic acid with methylcobalamin and vitamin B_6, methylcobalamin alone) on the metabolic pathway of homocysteiene. This analysis included the grouping variable, time course variable (prior, 2 and 4 h after methionine loading), and the interaction 'supplementation effect$\times$time course' as co-variables.

Baseline values of plasma tHcy concentrations at fasting, serum concentrations of folic acid, serum concentrations of vitamin B_6, vitamin B_{12}, and the proportion of methylcobalamin fraction of serum total vitamin B_{12} concentration in each randomized HD group were compared with those values of the normal control group by the Student's *t*-test. Post-treatment values of fasting plasma tHcy in each HD group were compared with fasting plasma tHcy values of the normal control group by the Student's *t*-test.

Results

All of the 21 randomized participants and 12 HD volunteers underwent baseline testing. No adverse events were reported during the treatment period. There were no clinical abnormalities following the methionine loading in any of the study participants. Additional details on participant recruitment and retention are provided in Figure 1.

Demographic and clinical characteristics

The demographic and clinical characteristics of each group are shown in Table 1. ANOVA revealed that there were no significant differences in baseline values of plasma tHcy levels and serum concentrations of folic acid, vitamin B_6, vitamin B_{12}, and the proportion of methylcobalamin fraction in total serum vitamin B_{12} concentration among the three randomized HD groups. There were also no significant differences with respect to age, HD duration, sex, haematocrit, serum urea nitrogen, serum creatinine, β_2-microglobulin, and albumin concentrations between the three randomized HD groups.

ANOVA also revealed that there were no significant differences in baseline values of fasting tHcy plasma levels, serum concentration of folic acid, vitamin B_6, and vitamin B_{12}, age, sex, haematocrit, serum concentration of urea nitrogen, creatinine, β_2-microglobulin, and albumin among the randomized HD patients and HD controls. The mean fasting plasma tHcy concentration (nmol/ml) in the HD patient groups overall ($n = 33$) was 22.3 ± 6.9, being significantly higher than in the normal control group (8.3 ± 1.9, $n = 7$, $P < 0.01$). Proportions of methylcobalamin fraction in the randomized HD patients ($n = 21$) ($48.1 \pm 6.4\%$) and serum vitamin B_6 concentration in the HD patient groups overall ($n = 33$) (2.9 ± 0.9 ng/ml) were significantly lower than in the normal control group (methylcobalamin $59.4 \pm 2.1\%$, $P < 0.01$; vitamin B_6 $21.9 \pm 11/6$ ng/ml, $P < 0.01$), while folic acid and vitamin B_{12} in the HD patient groups overall ($n = 33$) were not significantly different from the normal controls.

Effects of vitamin supplementation on serum vitamin concentrations in each group

Table 2 shows effects of vitamin supplementation on serum vitamin concentrations (folic acid, vitamin B_6, and vitamin B_{12}) in each group. Vitamin supplementation effectively increased serum concentrations of folic acid and vitamin B_{12} in each group of patients with supplements. Vitamin B_6 increased in group III only. Supplementation of methylcobalamin resulted in the remarkable increase of serum total vitamin B_{12} concentration, while the proportion of methylcobalamin fraction was not significantly changed in any group.

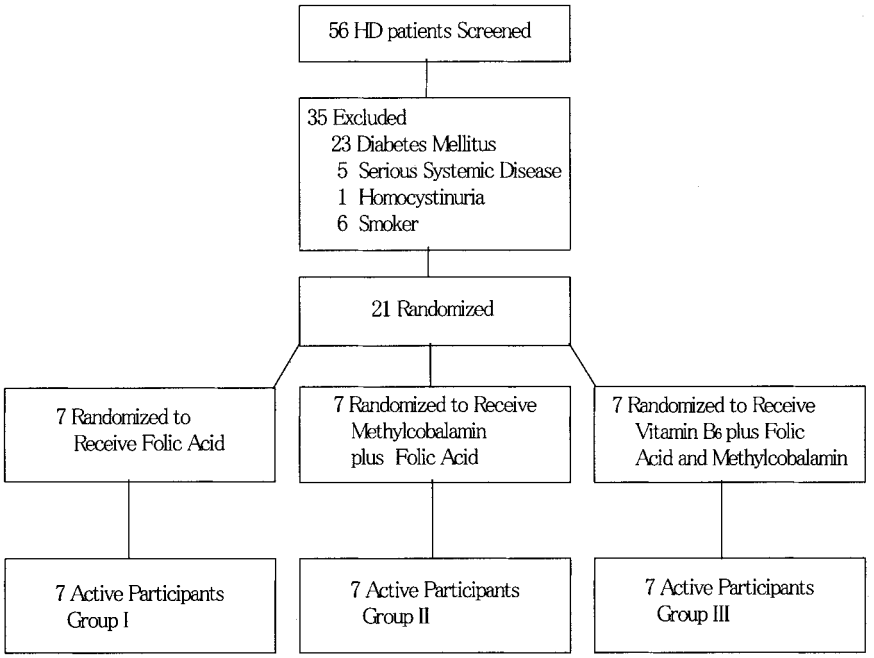

Fig. 1. Flow of participants of our randomized study.

Table 1. Baseline characteristics of HD patients and the normal control

	Normal control ($n=7$)	Group I ($n=7$)	Group II ($n=7$)	Group III ($n=7$)	HD control ($n=12$)
Supplement					
Folic acid		✓	✓	✓	
Methylcobalamin			✓	✓	✓
Vitamin B_6				✓	
Age (year)*	32±6	56±8	49±16	57±16	58±11
M:F*	5:2	4:3	4:3	4:3	7:5
HD duration (months)*		3±1.2	2.9±1.2	2.9±1.2	83.8±46.5
Cre (mg/dl)*	0.9±0.2	10±2.2	12.4±2.6	8.6±0.8	8.6±0.8
SUN (mg/dl)*	11.4±2.4	72.6±14.9	79.6±14.5	75.4±17.3	82.9±15.1
Ht (%)*	45±5.1	28.7±2.9	26.9±3.8	27.4±3.4	31.8±3.1
Alb (g/dl)*		3.8±0.3	3.9±0.3	3.8±0.3	3.9±0.3
β_2MG (μg/ml)*		23.2±7.3	25±3.0	21.3±5.0	28.8±5.8
Fasting tHcy (nmol/ml)*	8.3±1.9	19.2±2.9	20.9±5.7	21.3±7.3	25.6±8.4
Folic acid (ng/ml)*	8.2±2.3	9.9±2.5	7.4±2.0	6.4±2.6	8.7±2.6
Vitamin B_6 (PLP) (ng/ml)*	21.9±11.6**	2.7±0.5	3.3±1.0	2.9±1.0	2.9±1.1
Vitamin B_{12} (ng/ml)*	461±116	645±220	585±150	695±171	589±193
%m-B_{12} (%)*	59.4±2.1***	44.9±6.5	50.2±5.4	49.3±6.6	

*No differences were found among HD groups.
**Significantly higher than HD patients over all ($n=33$, 2.9±0.9 ng/ml, $P<0.01$).
***Significantly higher than the randomized HD patients over all ($n=21$, 48.1±6.4%, $P<0.01$).
Cre, creatinine; SUN, serum urea nitrogen; Ht, haematocrit; Alb, albumin; β_2MG, β_2-microalubumin; PLP, pyridoxal phosphate; %m-B_{12} fraction, proportion of methylcobalamin fraction.

Efficacy of vitamin supplementation on reducing plasma tHcy levels and findings of methionine-loading test (Tables 3–5)

Mean percentage reduction (per cent reduction) in plasma tHcy level were 17.3±8.4% in group I, 57.4±13.3% in group II, 59.9±5.6% in group III, and 18.7±7.5% in HD controls (Table 3). The reductions of plasma tHcy levels in groups II and III are both significantly remarkable ($P<0.01$). The power of the test to detect a reduction of plasma tHcy levels is 99.6% in group II and 99.9% in group III when type I error level of statistical analysis was set at $\alpha=0.05$. Post-treatment plasma tHcy levels (±95% CI) were 15.8±2.3 ng/ml (13.6–18.0) in group I, 8.3±1.4 ng/ml (6.5–10.0) in group II, 8.2±1.9 ng/ml (7.0–9.6) in group III, and 21.0±8.1 ng/ml (15.8–26.2) in HD control group. Group I and the HD control group showed significantly higher post-treatment fasting plasma tHcy levels compared with baseline

Table 2. Effects of vitamin supplementation on serum vitamin concentrations in each group

	After supplementation (baseline)	*P*-values*
Folic acid (ng/ml)		
Group I	all >15 (9.9 ± 2.5)	$P<0.01$
Group II	all >15 (7.4 ± 2.0)	$P<0.01$
Group III	all >15 (6.4 ± 2.6)	$P<0.01$
HD control	9.3 ± 3.2 (8.7 ± 2.6)	ns
Vitamin B_6 (ng/ml)		
Group I	3.3 ± 0.6 (2.7 ± 0.5)	ns
Group II	3.4 ± 1.6 (3.3 ± 1.0)	ns
Group III	26.2 ± 14.6 (2.9 ± 1.0)	$P<0.01$
HD control	3.2 ± 1.2 (2.9 ± 1.1)	ns
Vitamin B_{12} (ng/ml)		
Group I	696 ± 236 (645 ± 220)	ns
Group II	$50\,526\pm8888$ (585 ± 150)	$P<0.01$
Group III	$47\,048\pm7382$ (695 ± 171)	$P<0.01$
HD control	$56\,435\pm7382$ (589 ± 193)	$P<0.01$
%m-B_{12}		
Group I	44.2 ± 5.5 (44.9 ± 8.5)	ns
Group II	45.4 ± 11.2 (50.2 ± 5.4)	ns
Group III	42.3 ± 10.5 (49.3 ± 6.6)	ns
HD control		

*Compared with baseline by *t*-test. %m-B_{12}, proportion of methylcobalamin fraction.

Table 3. Treatment effect on reducing tHcy level in HD patients

Group	Mean reduction of tHcy by treatment (ng/ml)	Per cent (%) reduction in fasting tHcy by treatment	Power*
Group I	3.4 ± 1.8	17.3 ± 8.4	98.3%
Group II	12.6 ± 6.0	57.5 ± 3.3	99.6%
Group III	13.1 ± 5.5	59.9 ± 5.6	99.9%
HD control ($n=12$)	4.5 ± 1.8	18.7 ± 7.5	99.9%

*The power of the test to detect a reduction of tHcy level when type I error level of statistical analysis was set at $\alpha=0.05$.

Table 4. Post-treatment tHcy level and *n*/total (%) subjects with after tHcy levels <12 ng/ml

Group	After treatment fasting tHcy level (ng/ml) (95% CI)	*n*/total (%) subjects with after treatment tHcy levels <12 ng/ml	*P*-value*
Group I	15.8 ± 2.3 (13.6–18.0)	0/7 (0%)	$P<0.01$
Group II	8.3 ± 4 (6.5–10.0)	7/7 (100%)	ns
Group III	8.2 ± 9 (7.0–9.6)	7/7 (100%)	ns
HD control	21.0 ± 8.1 (15.8–26.2)	1/12 (12%)	$P<0.01$

*Compared with baseline of normal control (8.3 ± 9 ng/ml) by *t*-test. CI, confidence interval.

(of the normal control group) ($P<0.01$) (Table 4). Treatment resulted in normalization of fasting plasma tHcy levels (<12 ng/ml) in all 14 patients treated by combined administration of methylcobalamin and supplementation of folic acid (groups II and III) regardless of whether there was supplementation of vitamin B_6. None of the seven patients with only supplementation of folic acid and one of 12 patients supplemented only with methylcobaramin experienced normalization of fasting plasma tHcy levels (Table 4).

Plasma tHcy levels were significantly elevated after methionine loading, but the increases were suppressed by vitamin supplements in groups II and III. The presence of interaction between time course and supplementation in groups II and III clearly indicates that increases in plasma tHcy level by methionine loading were suppressed by the combined administration of methylcobalamin and supplementation of folic acid (Table 5). Groups II and III showed normal methionine loading test results after treatment.

Discussion

From this study we should make special note of the fact that, in HD patients, the hyperhomocysteinaemia, which has proven quite refractory to pharmacological doses of folic acid supplementation [16,17], is cured by co-administration of methylcobalamin and high-dose folic acid supplementation. This method of therapy for hyperhomocysteinaemia could combat the risk associated with atherosclerosis and cardiovascular disease in patients with CRF.

Folate is vital in humans for several metabolic reactions involved in the formation and transfer of one-carbon units, such as formyl, methylene, or methyl ($-CH_3$). In the remethylation pathways a methyl group is transferred from 5-methl-tetrahydrofolate, a folate-related derivative, to produce methionine. In our study, the fasting plasma tHcy concentration was reduced 17 ± 8.4% by supplementation with high-dose folic acid. Our results were similar to those of Bostom's study and support the Vienna Multicenter Study, which clearly demonstrated that hyperhomocysteinaemia in end-stage renal disease patients cannot be cured solely by folic acid supplementation [18]. Supplementation of L-5-methyltetrahydrofolate did not prove to be any more beneficial than folic acid in treating hyperhomocysteinaemia [5].

Administration of methylcobalamin, which is co-enzyme in the methionine remethylation pathway, was anticipated to be another strategy to cure hyperhomocysteinaemia. Our study has indicated that administering methylcobalamin alone to HD patients was not sufficient to normalize hyperhomocysteinaemia in CRF. That result supported our consideration that methylcobalamin would require a sufficient amount of intracellular of L-5-methyltetrahydrofolate in remethylation. Vital processes in folate disposition, however, also include intestinal absorption and receptor and carrier-mediated transport across cell membranes. And, it is known that the $677C\rightarrow T$ transition of methylene tetrahydrofolate reductase is the cause of hyperhomocysteinaemia. Arnadottir *et al.* reported

Table 5. Plasma tHcy levels after methionine loading test

	Vitamin supplementation						*P*-value by ANOVA		
	Before supplementation time course			After supplementation time course			Effect		Interaction (A × B)
	Fasting (0 h)	2 h	4 h	Fasting (0 h)	2 h	4 h	Time course (A)	Supplement (B)	
Group I	19.2 ± 2.9	23.8 ± 3.9	28.2 ± 4.4	15.8 ± 2.3	20.0 ± 2.9	23.9 ± 3.6	$P < 0.01$	ns	ns
Group II	20.9 ± 5.7	26.0 ± 6.3	30.4 ± 7.5	8.3 ± 1.4	11.6 ± 1.7	14.0 ± 2.4	$P < 0.01$	$P < 0.01$	$P < 0.01$
Group III	21.3 ± 7.3	26.4 ± 8.4	31.1 ± 9.4	8.2 ± 1.9	11.1 ± 2.6	13.6 ± 3.1	$P < 0.01$	$P < 0.01$	$P < 0.01$
Normal control*	8.6 ± 1.7	12.3 ± 2.3	14.0 ± 2.5						
HD control	25.6 ± 8.4	30.9 ± 9.4	36.2 ± 10.6	21.0 ± 8.1	25.8 ± 9.2	30.7 ± 10.5	$P < 0.01$	ns	ns

*$P < 0.01$ *vs* HD groups before supplementation. Homocysteine elevations after methionine loading in groups II and III were normalized by vitamin supplementation. No significant difference among HD groups (groups I–III, HD control) before supplementation.

that, at a folic acid dose of 15 mg/week, red blood cells approached folate saturation and the maximum effect on tHcy seemed to be obtained at that dose in HD patients [19]. Bostom *et al.* indicated that, in comparison to high-dose folic acid (15 mg/day), high-dose oral L-5-methyltetrahydrofolate-based supplementation (17 mg/day) did not afford improved tHcy-lowing efficacy among HD patients [5]. Plassmann demonstrated that supplementation of 15 mg/day folic acid resulted in the maximum effect on lowering tHcy regardless of type of MTHFR genotype (677CC, 677CT, or 677TT) [18]. These studies indicated that the body cells could be saturated with L-5-methyltetrahydrofolate by supplementation with 15 mg/day folic acid regardless of the type of MTHFR genotype.

Homocysteine loading is considered to be the most effective method to assess the quality of the remethylation pathway [20]. Taking into account that homocysteine is a candidate uraemic toxin that affects cardiovascular risk, we inferred that homocysteine loading may not be suitable for the patients in this study. HD patients have shown an exaggerated increase in plasma tHcy level after methionine loading, and because their trans-sulfuration pathway activity was reported as not significantly decreased [4], the methionine loading was, therefore, considered to be more appropriate to evaluate the quality of the remethylation pathway in uraemic patients. We elected to load half of this diagnostic dose of methionine (50 mg/kg), which was a sufficient loading dose to achieve our objective for this study.

Our study suggested that both supplements of high-dose folic acid and methylcobalamin are required for the remethylation pathway to regain its normal activity. Based upon these results, we deduced that deterioration of the remethylation pathway is related not only to an inhibition of folate enzymes but also to a deficiency of methylcobalamin in uraemic patients.

Vitamin B_{12} has several analogues: cyanocobalamin, hydroxycobalamin, deoxyadenosylcobalamin, and methylcobalamin. Each fraction can be estimated by measuring the proportion of that fraction of the serum total vitamin B_{12} concentration. The prevalence of these analogues, and their metabolism, has not been elucidated clearly. Wilson *et al.* reported that an increase in the proportion of the cyanocobalamin fraction indicates accelerated cyanide (CN) detoxication via cyanocobalamine synthesis [21]. We reported previously that the ability to detoxify CN is impaired by reduced renal function [9]. In that study, we indicated that vitamin B_{12} is utilized to detoxify CN, resulting in an increase in the proportion of cyanocobalamin and a decrease in the proportion of methylcobalamin. Based on our results, we can deduce that deficiency of methylcobalamin could be induced by deterioration of renal function.

The accumulation of homocysteine in CRF patients causes the hydrolysis of *S*-adenosylhomocysteine (AdoHcy) to slow down, resulting in accumulation of *S*-adenosylhomocysteine (AdoMet) and decreased AdoMet : AdoHcy ratios [22]. The concentration of AdoHcy, and even more importantly the ratio of AdoMet : AdoHcy, exert their potent inhibitory effect on the transmethylation reaction [23]. Because methylcobalamine is synthesized through a transmethylation reaction [24], the proportion of the methylcobalamin fraction, therefore, decreases with the accumulation of homocysteine. Through these mechanisms, the hyperhomocysteinaemia and the deficiency of methylcobalamin become a vicious cycle.

Cyanocobalamin has to be changed and transmethylated into methylcobalamin to act as a co-enzyme. This methylcobalamin synthesis is inhibited by accumulation of AdoMet, hence we deduce that methylcobalamin is more potent than cyanocobalamin for reducing plasma tHcy concentrations in uraemic patients.

In our study, the proportion of methylcobalamin fraction was not changed, while serum total vitamin B_{12} concentration increased remarkably after i.v. methylcobalamin administration. This result indicates that administered methycobalamin supplied its methyl group and was changed into other analogues of vitamin B_{12}. It can be inferred that a decrease in plasma tHcy concentrations would accelerate transmethylation reactions.

Statistically, the effect of methylcobalamin administration along with folic acid supplementation in lowering plasma tHcy concentrations was considered to be remarkable. However, in our study the patient number in each group was very low. Therefore, our results should be confirmed by a large study, including an adequate number of patients.

In conclusion, plasma tHcy concentrations are normalized by combined administration of methylcobalamin and supplementation of high-dose folic acid in HD patients. Our study suggests that both supplementation of high-dose folic acid and methylcobalamin are required for the remethylation pathway to regain its normal activity. This treatment for hyperhomocysteinaemia could be a therapeutic strategy to combat the risk associated with atherosclerosis and cardiovascular disease in patients with CRF.

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Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903
Email: toni.hailmanAfda.hhssiov

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

RE: Docket FDA-2015-N-3534,

Methylcobalamin Dear Ms. Hallman,

McGuff Compounding Pharmacy Services, Inc. (MCPS) is responding to the FDA's questions to the nomination of Methylcobalamin inclusion on the 503A bulk drug substances list due by Feb. 23, 2018.

Responses:

Q. To the extent possible, we request that you submit information regarding the historical use of compounded methylcobalamin, such as the approximate number of prescriptions per year for compounded methylcobalamin and the uses associated with those prescriptions for compounded methylcobalamin.

A. Historically, MCPS has dispensed an average of 13,112 prescriptions annually for various compounded preparations of methylcobalamin as follows:

Formulation Strength & Size	Avg Annual Prescriptions Dispensed
Methylcobalamin 1 mg/mL 1mL	53
Methylcobalamin 1 mg/mL 5mL	782
Methylcobalamin 1 mg/mL 10mL	252
Methylcobalamin 1 mg/mL 30mL	7,029
Methylcobalamin 5 mg/mL 10mL	1,074
Methylcobalamin 5 mg/mL 30mL	3,923

Pharmacies aren't required to document the associated use with each prescription. Some associated uses of compounded methylcobalamin include autistic spectrum disorder, diabetic neuropathy, pain management, amyotrophic lateral sclerosis, and as a conjunctive therapeutic agent in hemodialysis patients.

Individual Patients' Statements (Names Removed To Protect Identity): For the last few years I have been using injectable Methycobalamin prescribed for me from my naturopathic physician and provided by a compounding pharmacist. I have been diagnosed with fibromyalgia/chronic fatigue for over twenty years. Following my naturopath's advice has helped me considerably over the years but it is this vitamin that has allowed me to
exercise once again and function, not just normally, but with some of the zest that I have observed in others, that I previously could only dream of.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 7 14.438.0520
EMAIL: answerstmcguff.com
WEBSITE: www.mcguff.com

Being able to have this medication/supplement with convenience has made a world of difference in my life. It is safe and effective and reasonably priced. Compounding pharmacists are professionals that have the expertise to make sure these supplements/medications remain safe and effective and will work with physicians that approach health from a different perspective than the conventional/industrial medical model.

I am grateful for access to methycobalamin through my compounding pharmacist and will be watching the FDA and will be in contact with my elected representatives in support of preserving that access.

My name is ******* and 6 years ago I was diagnosed with chronic fatigue due to the Epstein Barr virus that had been lying dormant in my system, likely since I was a teen. I have an abnormally low white blood cell count and get sick very often because I just don't have a strong enough immune system to fight off all of the viruses that I come in contact with.

After giving birth to my son, who was born with health problems and had to be fed small amounts every 30 minutes around the clock, I was sleep deprived and my immune system completely failed me. The Epstein Barr virus took over my system and I was eventually so weak that I could not get out of bed and function normally even to care for my son. After getting tested for many things, the source of the chronic fatigue was discovered and I began a regimen of methylcobalamin injections along with a strict diet that reduced inflammation. The improvement in my quality of life has been dramatic. Although I still have occasional episodes of fatigue, I am able to perform my tasks as a mother and continue to earn an income.

Occasionally, if my compounding pharmacy is out of stock of methylcobalamin, I have to go without while I wait for it to be restocked. Without the injections, I slip into deep states of fatigue that take sometimes weeks to fully recover from. At this point, this is the only treatment that I have been able to live a somewhat normal life with the help of. A future for myself and my child without the help of methylcobalamin is frightening. A life of unemployment and disability would likely be my path if I were not able to receive the regular injections. Eventually with a poorly functioning immune system, I would be susceptible to contracting an even more serious illness and would not have the defenses to fight it off. As a single mother, there's nothing more frightening than having your child be left without a parent.

Please consider how devastating it would be to countless others who rely on access to methylcobalamin to live a normal life. I appreciate your time in reading my testimony and hope that you will look through a compassionate lens as you make this decision that affects so many.

I have suffered from chronic fatigue for many years. Five years ago my personal physician prescribed Methylcobalamin shots, which improved my energy level significantly. This benefit has enabled me to remain active in retirement.

I am a 68 year old mainly healthy woman with many food intolerances. One of the side affects of not having lots of food options and getting the nutrition that I need from these missing foods, is my ability to think clearly.

Since starting the methylcobalamin I have been able to think clearly and my life is back to normal. Without this drug I am concerned that it will put me

into a position of not being able to function properly and not be able to work and care for myself as a normal person with cognitive thinking skills.

Please do everything you can to keep this available.

I am a clinical nutritionist in private practice for 22 years.
METHYLCOBALAMIN injectable is ESSENTIAL to many of my clients, including myself, my daughter, AND my office manager. Oral preparations of cyanocobalamin OR methylcobalamin do NOT work for us. We have tried! No one wants to do injections unless that is the only best option, which it has proven to be in so many cases. We have all tried oral preparations first, and know the differences.

The benefit to our overall health is immeasurable with the availability of MethylB12 injections.

Please to not restrict access to this essential nutrient.

Please allow patients to have access to Methylcobalamin. I have a gene mutation and other illnesses that are greatly improved by this simple treatment. Were it not to be available to me with my physician monitoring me in its easy, inexpensive, form I would not be able to take it. That would impair my health making me less available to work and take care of my child.

When I was first diagnosed with a B 12 deficiency my B 12 level was 140 and at first I was given cyanocobalamin injections at my doctors office once a month. I had one of the first gastric bypass is 1975 so I cannot absorb B12 sublingually I have to have injections for the rest of my life. It only took 30 years for somebody to recognize this because most my doctor said there was no such thing as a B 12 deficiency!

Getting and then ejection of cyanocobalamin once a month did nothing for me didn't even raise my levels so my doctor increased to twice monthly. I kept asking her why I didn't feel any different and my level still didn't go up? So she increased it once weekly and my levels went up but I still didn't feel any different and I didn't realize I was getting cyanocobalamin and how bad it is for you and most people cannot convert it.

She finally agreed to write me a prescription four hydroxycobalamin because she said there was no such thing as methylcobalamin. I took that for year and it did nothing except keep my blood serum level high which if you have been supplementing at all your blood serum test is worthless!
Then my PCP I should say my third one sent me to a hematologist because I needed infusions. And she took over monitoring my B 12 levels and she's the one that told me the blood serum test was worthless and did a methylmalonic acid test and my levels were too high way too high!
That's what I discussed with my PCP who writes my prescription for my Methylcobalamin to please write me a prescription from a compounding pharmacy! Within about three months my methylmalonic acid test was optimal. I see her every four months to monitor my ferritin and B 12 levels and as long as I inject every other day I can keep my methylmalonic acid test optimal. But every time my blood serum test posted on my chart my PCP would say my levels was too high? She didn't understand that a blood sermon test is always going to register at the highest level if you are supplementing. So I discussed it with my hematologist and she stopped running that test completely because she even said it was worthless. I didn't want to take the chance of my PCP stopping my injections because she didn't understand B12. She also doesn't understand that I cannot absorb it because of my stomach surgery three times and will have to inject for life.

I had neuropathy so bad I couldn't hardly walk I was in so much pain I even had foot surgery and all it was a B 12 deficiency.

I need methylcobalamin due to my homozygous 677 genetic mutation. Supplementing with bi monthly injections keeps me functioning well.

Please allow continued access to this supplement.

I am deeply disturbed by the news that the FDA is reconsidering the distribution/and or formulation of Methylcobabamin. After blood tests came back with suspicious chronic inflammation my doctor ordered genetic testing from 23and me and the results came back showing that I have a genetic defect in my methylation cycle and I am compound homozygous....without a degree in biology I have a limited understanding of how it all works but what I DO know if that without this critical enzyme process my body isn't equipped with the tools that it needs to carry out basic metabolic repair to my dna and without supplementation of L-methylfolate in combination with injections of methylcobalamin (both needed in conjunction in order to convert folate and folic acid into its biologically active form) my homocysteine levels will constantly be elevated(regardless of diet and exercise) and I will be at a SIGNIFICANTLY high risk for a host of deadly diseases (heart disease and stroke being the top of the list).

I am asking for your deep consideration on this review as my actual life depends on this product being available. I exercise daily and eat only organic fresh/unprocessed clean food...I am doing everything I can to live a healthy toxic free life and I would hate to think that the FDA would eliminate such an immensely important part of the process that keeps people like myself alive and well.

I dont imagine you get many of these letters ...genetic testing and medicine is still relatively new (at least to lay people like myself). But I am CERTAIN that I am not alone in this. Please help people like me achieve our optimum health and keep us OUT of the hospital and into our early graves.

Thank you for your time.
Apologies for the terrible grammar.

Here is my story…

I do not absorb any form of vitamin B and after 5 years of trying anything and everything my Doctor could think of she finally prescribed Methylcobalamin. My numbers finally stabilized, which was important since I have a tendency to get very sick from colds and flu compared to most people. Last year we reduced my dosage in half to see how I would do and I had six colds from December to May and had to be given antibiotics twice. Since we reinstated my dose I have had one small cold.

I am an athlete and I train for my sport several times a week, it has also given me stamina and energy to keep up on my workouts. I want to remain healthy and active as long as I can. I am turning 50 this year and hope that the FDA recognizes the benefits of Methylcobalamin. Every person is only as good as their chemical make-up and mine (and many others) are in need of this to help support and stabilize their personal inner chemistry.

With fibromyalgia and other health issues causing me to be fatigued 24 hours a day and sleeping my life away, my doctor recommended Methylcobalamin. It has given me a significant increase of energy and helped me to be able to function much more normally.

This is a safe product that should be easily accessible to all who need it.

Regarding my use of Methylcobalamin. Until I started using Methylcobalamin, I suffered with deep and debilitating depression. I had thoughts of suicide on a regular basis. Since beginning the use of Methylcobalamin, I no longer suffer from depression at all. The use of this product has been a life saver for me.

Sincerely,

I use methylcobalamin injection to treat megaloblastic anemia, without it I suffer from severe fatigue and anemia related issues. Due to malabsorption the injections are the only way in which I can receive enough methylcobalamin to relieve my symptoms.

“I have a rare neurological disorder. One *given* to me as the end result of medical mistakes in the emergency room. It involves the myelin sheath surrounding my nerve fibers. While good nutrition is an important first step in my daily routine; it is impossible for me to ingest the amount of B12 needed for tissue repair through food alone. Methylcobalamin injections are a critical part of my recovery. As it is immediately available to my immune system and tissue my body can continue to concentrate on its recovery rather than conversion of an inferior product. If it is no longer available I will regress. I will no longer be able to participate in my community in the small way that I do nor will I ever have the hope of ever becoming a *full member* of society again. Methylcobalamin is a crucial part of my recovery.

While I respect the FDA and it’s concern for products that harm patients, I am more concerned that this is a push by large drug manufacturers to get rid of something that affects their bottom line. Much as vitamin C was discovered to prevent scurvy the effects of B12 are well known to help neurological disorders. Whether it’s a stroke, a brain injury from concussion or multiple sclerosis; B12 is a building block for repair. “.

I am a patient who uses Methylcobalamin for B12 deficiency. I was diagnosed with B12 deficiency eight years ago. At the time it was unknown what was wrong with me, I had severe symptom including nerve damage throughout my body. After numerous labs, x-rays, MRI’s, etc. that costs thousands of dollars, I was finally diagnosed with B12 deficiency. I was started on a B12 protocol to increase my B12 stores. I was given injections of Cyanocobalamin at my doctor’s office in high dosages over a period of a couple of months. My B12 stores rose but my symptoms did not improve, especially my nerve damage. I could barley walk without being in excruciating pain.

I started doing extensive research and found the best and highest quality B12 to use was Methylcobalamin, particularly for nerve damage. My doctor then prescribed me with Methylcobalamin through my compounding pharmacy and I began self-injections twice a month at home. Within weeks my never damage started healing. Within a year I was completely healed of any nerve damage. I attribute this to the use of high quality Methylcobalamin.

I will need to give myself injections of Methylcobalamin for the rest of my life. I cannot take oral Methylcobalamin because I do not absorb B12. I cannot go to my doctor’s office for it because their protocol is Cyanocobalamin and from my research and my own experience I know this does not work for me. If they did offer it, it would cost me time and additional money I cannot afford in

order to go to the doctor's office every other week to get my life saving injections.

Making it so I cannot receive Methylcobalamin through my compounding pharmacy would cause a disservice to me and be a detriment to my health and I am sure many others will suffer as well. It is important that patients who suffer with B12 deficiency have access to Methylcobalamin in a safe way through our trusted compounding pharmacies.

Thank you for your time.
Sincerely,

I have been taking injections for at least 2 Years. My energy and quality of life would be greatly affected if I couldn't get my injections of methylcobalomin. I suffer from fibromyalgia, and
Arthritis and back pain.

Thank you

I am a Lyme disease survivor with a methylation cycle that is very broken. I had take C form of B12 because that is all me regular doctor would give me. Taking Methyl B12 saved my life. Between my horrible methylation cycle and the manner with which Lyme kills mitochondrial system I would not be where I am today without Methyl B12.

Sincerely,

I have been using injectable methylcobalamin for the last 20 years as treatment for megaloblastic/pernicious anemia.

There is no other treatment for this condition and without it I suffer from severe symptoms— ones that can potentially lead to brain damage. In that sense it is a preventive treatment for conditions that can become a huge burden on the healthcare system.

Thank you for your attention— I am asking that methylcobalamin remain available to patients like myself.

FDA PLEASE DON'T DO AWAY WITH methylcobalamin

My name is (b) (6) and I am responding to an injectable b12
My mother and I have pernicious anemia and would die without injection B-12. I was injecting Cyanocobalamin for 20 years with many fluctuations in my levels, most of the time very low.
My Doctor (b) (6) recommended methylcobalamin which has made all the difference by stabilizing my B-12 levels. Dr. (b) (6) also informed me of a chemical in Cyanocobalamin that could store in my brain and cause damage later on. I did the research myself and was very grateful for the recommendation from Dr. (b) (6)

Please do not pull Methylcobalamin from the market. As someone who suffers from a couple of chronic conditions, this product is safe, affordable and effective. Not sure I could face Monday mornings without my weekly injection. Please allow it to be available to those of us in need. Thank you.

Please be advised that I and my husband have used methylcobalamin Injections for several years. We benefit greatly with weekly injections as a mood stabilizer and we experienced better absorption within your tissues as our homocysteine level was in normal ranges.

I've been using compounded Methylcobalamin for five years now and for me it has been a life saver. I am now combining the Methylcobalamin with MTHFR and the combination has really been useful by improving my energy level which is low due to my having Hemochromatosis. I suffered for years with low energy and fatigue and as I've stated Methylcobalamin above my life has changed drastically for the better. Please keep this compounded drug available for those of us that whom have showed improvement and do not want to regress back to feeling hopeless.
Please do not take this drug away.

I have 2 mutated genes which prevent me from absorbing methylcobalamin (vit B12) through the gut. This is absolutely life-threatening to me.
In the past, before I knew about my inability to absorb B12, I was a bronzed orange color with liver failure. Very life threatening. All my life I've known something was wrong with my system, but now I know I can't live without methylcobalamin.

Please do not discontinue this very necessary injection. It's only since I've taken these injections every other day that I can sleep at night and I can absorb the proper nutrition.

Thank you so much!

My doctor placed me on this type of b12 after my breast cancer dx in 2011 as I was low and had thyroid issues along with other health issues that are resolved now due to his diligence and my cooperation. I eat a vegan whole food plant based diet (according to JAMA this is the best diet for a cancer patient),therefore I need to take supplemental B-12. I also have a MTHFR gene mutation that means I need this type of B12 as the synthetic, non methyl type does not work for me. Please continue to provide this important nutrient to those of us who need. There are many, many more medications that are harmful that could be discontinued. This is not one of them.
Thank you for your consideration.

Please do not take this off the market or make it unavailable. I have an absorption issue that has not been solved. I did injections a couple of years ago and it helped. I was off injections and tried some tablet but only the injections of Methylcobalamin worked so I am now on them 2 times a week and we are seeing progress. I hope to stay on this for the rest of my life. Why take something that works well away??? My only conclusion is that Big Pharma wants to own it all and is jealous that NDs and Compounding Pharmacies are helping people when some usual methods have not.

I had pernicious anemia and digestive disorders which resulted in a severe B12 (Methylcobalamin) deficiency. Having digestive disorders resulting in food malabsorption greatly reduces the body's ability to absorb B12 through oral admimistration. I am also a vegetarian due to food allergies and this greatly reduces the amount of B12 available through natural means. The injectable form must remain available and is essential for the many thousands of people who suffer with these types of disorders; without it, there would undoubtedly be deficiencies, possibly quite severe, and the human body cannot survive without it.

We read recently that the FDA is reviewing the medicinal use of Methycobalamin, and is currently considering discontinued access to Methycobalamin through compounding pharmacies. We are alarmed at the prospect of no longer receiving this therapy because it has profoundly improved the health of 3 members of our household. My husband, my son and I all suffer from methylation issues related to genetically inherited methylenetetrahydrofolate reductase (MTHFR) C677T mutation. We are all homozygous genotype. Until about 5 years ago, my husband and I suffered from extreme fatigue and “brain fog", making it very difficult to face the daily demands of our lives.

Our son suffered the same issues, compounded by anxiety and depression. When our doctor diagnosed our MTHFR genotype and started our regimen of Methycobalamin injections, we all felt an immediate and dramatic improvement in our energy levels, our mental acuity and, in the case of my son, his mood. In fact, we can always tell when he has not been consistent with his injections because he become morose and irritable. The difference is so profound, it is as if a light switch has been turned on and off. We hope you will consider the many people who suffer from MTHFR and who benefit from this very effective treatment so that we can continue to have access to it through our compounding pharmacies.

Thank you,

I have used both methylcobalamine and cyanocobalamine and strongly prefer methyl. I have had weekly B12 shots for many years due to a medical condition and ask that it remain available.

Hi, I have MS, and Methylb12 helps my mobility, fatigue is less, pain is less. Please keep this RX available for all patients, especially MS people. RRMs for 22 years, Methylb12 injections brought me back from wheelchair, I depend upon b12 to keep moving without pain.

Thank you

When I miss my injections of methylcobalamin (1-2 x per week) my nerves feel raw, I become physically and emotionally fragile, and I suffer with facial neuraneuralgia. (b) (6)

Thank you for bringing the issue of the potential FDA action against methylcobalamin to my attention.

Continued availability of this compounded injectable drug is imperative to my health. I have a genetic defect that impacts absorption of Vitamin B-12. I do not fully understand the chemistry, biology, or genetics of my condition. I do know that without access to injected methylcobalamin, I will suffer from debilitating exhaustion and reduced mental acuity to say the least. I have come back from that state and I do not want to return to it.

In 2009, I was struck down with debilitating exhaustion. Though I consulted with multiple doctors, some of whom revealed a small portion of the puzzle, the final piece was not found until 2012 when my current doctor discovered the genetic defect. She began treatment with regular methylcobalamin injections. I do not enjoy it but I administer the injection to myself on a weekly basis. On those occasions that I have forgotten and delayed a few days, I can barely drag myself through the house.

I would rather be a contributing member of society as I am now rather than a dependent. Please do not remove this medication/compound from the lives of those of us who depend upon it.

On (b) (6) 2015 I came down with the most prolific illness of my life. I remember the day because I missed my friends wedding party. I was horribly fatigued and over the next two months at least one dermatome of my body and face was swollen and itchy. No one could figure out what was going on. I couldn't work, I couldn't sleep. I went on a three day fast/ cleanse, drinking only lemon water and resting to reset my system. I had done this before when I was very ill and had always felt better after. This time I felt worse. I suffered from extreme high blood pressure and heart rate since I began to feel sick, my normal resting hr was around 60 and it was up to above 100 on average. I was tested for all kinds of things, the allergy specialist told me I had "hives" and sent me away with benadryl and montelucast. Nothing would work. I found that a large dose of valcyclovir (4g per day) was the only thing that would take away my symptoms. It was like I was having a swelling and rashing shingles that would not turn off. My neuroendocrine system was haywire. Fast forward two years and I had begun to feel better but would only be symptom free for a couple days at a time, although the symptoms had finally calmed down and only would flare up extremely about once a month. I was still on 4g of valcyclovir per day. I had had enough and was feeling well enough to try to go off the antivirals. A few weeks later I had a week of biking and yoga that gradually wore me empty of energy. At the end of the week I could feel the skin around my neck and head crawl and was having severe muscle twitches. I had a friend mention B 12 shots and I thought I should try them. I took 20,000 mcg of cyanocobalamin injections over the course of 4 days before the symptoms went away. I am in a healthcare profession and have had graduate training in nutrition, so I was interested to research what may be going on with my body. I had done extensive research regarding my symptoms for nearly two years, since the onset that summer in 2015. The best I could reason was that latent viruses were being reactivated in my nervous system; but why? The B12 "crash" I had after a week of moderate athletic activity held the clue... I had known that I have mutations in my MTHFR genes from a 23 and me test years ago. If my body was using all it's B12 reserves to detoxify from an environmental toxin, then that could be demyelinating my neurons and causing latent viruses such as HHV6, Parvovirus B19, Varicella Zoster, and others to show symptoms again, after years of latency... I thought of that summer that I got sick and remembered I had an amalgam filling replaced that had had some decay under the original mercury filling. The young dentist did not use best practices and just started drilling, no dental dam, no vacuum, no protection from the mercury dust that toxified my system. I called the dental office and the date of the procedure was the afternoon of (b) (6) 2015, one and a half days before my 'illness' set in. I was poisoned. After finding this link, I started taking Methylcobalamin injections, 5,000 mcg every other day. I have been on this regimen for 7 months, along with Chelation IV that started 4 months ago. Now I can go up to 3 or 4 days with out an injection, but I still need at least two a week, and during times of high stress, I need more. I am free of prescription meds and on my way to detoxifying from the horrible mercury and finally starting to feel more like myself again. I don't know where I would be without methylcobalamin and I with insurance companies would pay for my treatments. These injections as well as my chelation IVs. That is the ONLY healthcare I have and I have to pay out of pocket. Being that I am self employed and have not worked enough the past two years because I was poisoned, this matters to me. Thankfully the methylcobalamin is reasonably priced.

Please keep producing this!

Sincerely,

My personal experience is that without injections of methylcobalamin, I simply don't have any energy. At the age of 67, I still work 37 hours a week, and I need that job. I wouldn't have the energy to do it if I didn't have methylcobalamin. When I don't get it, I simply fade. It would literally change my life for the worse if methylcobalamin weren't available.

Good afternoon. I strongly urge the FDA to recognize the extreme importance of methylcobalamin, and to continue to allow compounding pharmacies to manufacture these prescriptions.

In my case, I become B-12 anemic if I don't have the methylcobalamin 1x a week in injection form. In my case, I eventually become iron anemic, and suffer gastrointestinal issues, as well as fatigue symptoms. Injection form is absorbed by the system quicker and more efficiently than oral B-12, henceforth allowing the body to utilize its properties more effectively.

B-12 is responsible for a plethora of inner workings in the body, neurologically, mentally, physically, etc. Methylcobalamin is a safe way for patients to receive the amount of B-12 they need by most effective means possible.

I implore the FDA with great urgency, to take into a careful and mindful consideration, just how much impact removing methylcobalamin from the capable and talented hands of compounding pharmacists, such limiting greatly a patient's access to what they rely on to operate as healthy an individual as possible, will have on the community of patients who so desperately depend on this concoction to get along in their daily lives.

Thank you.

I have peripheral neuropathy and pernicious anemia. I am not an expert on drug compounding and do not know of alternatives; but I have been using methylcobalamin twice a week subQ for some time with absolute tolerance.

I understand there is a possibility that this will be regulated off the market. I would prefer that the PCAC leave well enough alone.

I am 75 years young and my quality of life would be impaired considerably if I was no longer able to obtain Methylcobalamin. I have been prescribed it for many years by my doctor, who is an M.D. with no less than three Board Certifications.

Methylcobalamin gives me energy, protects nerve and brain cells, supports immune function, and helps me maintain a positive outlook.

I trust this important nutrient will continue to be available to me always.

Thank you

My name is ***, I am a 62 year old woman who was diagnosed with PERNICIOUS ANEMIA in my early twenties.. My mother had this as well, yes it is hereditary. For twenty some years I took sublingual injections 1/2 cc once a week of CYANOCOBALAMIN, without feeling any results, good or bad, So I did my homework, researched my options to learn there were other types of B-12 out there. I tried METHYLCOBALAMIN, on the

suggestion of my pharmacist and my preferred provider. It's been close to twenty years now. I can what's most important to myself is to be able to hold a conversation with adults and not sound stupid.

So after reading what the intentions of this committee wants to do is to remove this drug from the thousands that have had fantastic results and can now live a full life without the embarrassment of feeling and sounding stupid. Who wanted or suggested this idea anyway?

The known facts that METHYLCOBALAMIN
Helps avoid Alzheimers and Multiple Sclerosis
Improves Sleep, also lowers potentially toxic levels of amino acids
Also protects the brain and Nervous System
Sublingual administration of B-12 is the BEST CHOICE, because it bypasses the digestive tract.
So to be clear, without taking my weekly B-12 shot, I do this myself, have for years. My husband sometimes gives it to me. Anyone can give a shot. Speaking with any adult dialect is almost impossible, as I can't remember what was said previously, so hence I repeat myself a lot, very noticeable. Not to mention, when talking I think of a word I want to say and a whole new word comes out.
I cannot add 2 and 6
Don't remember where I parked at the grocery store
Don't sleep well

Memory is absent, age takes it toll but without Methylcobalamin you can't even dream of the daily frustration I experience. Functioning In the real world with any sort of job outside the home would be next to impossible without Methylcobalamin.

I choose not to be a living experiment trying other B-12 medications. I am not a robot, I can read about the others and I choose Methylocobalamin to improve my health and life as I now know it. My health is manageable as I take care of myself to the best of my ability, eating healthy and keeping my weight in check.

PERNICIOUS ANEMIA left untreated can have horrific intolerable results. Should your committee want to be responsible for the thousands of people who will suffer severely due to your choice not to continue making Methylcobalamin accessible, to those who need it. We have only ourselves to blame how we live and treat others, I can't imagine how anyone could sleep at night doing such a horrible injustice to people both young and old. This world can definitely use a few more honest, healthy people who can live self sufficiently within thereon minds. Without Methylcobalamin there will no doubly thousands of people like me walking around wondering who they are, and where there going and what they did and why. Maybe putting us all on a leash would cure Pernicious Anemia. Looks like your committee will be the ones holding the leashes.
Just one voice please hear me, no one should feel like the mind is slipping, but with Methylcobalamin it's manageable, with out it's intolerable.

Thanks for listening, I hope you won't restrict my senior years by not allowing myself to take care of me. If you choose to discontinue Methylcobalamin the worlds population will surely suffer with no one to blame but you. So sad.

Please dont discontinue this medication! It saved my life! After being diagnosed with a severe b12 deficiency, and no other forms of b12 working, i was put on this compounded medication. My vertigo of twenty years, which left me unable to drive, disappeared! My daily migraines gone! My panic attacks, gone! It truly Saved. My. Life. If i do not have this medication, my life

will be over! Im begging you to reconsider the importance of this medication!
Sincerely *****

It has come to my attention that the following compounds are being considered to be restricted by the FDA. I beg you to please not do this. These compunds:
Methycobalamin, Quercitin, Reduced L- Glutathion, Alpha Liponic Acid, Choline Chloride and many other naturalpath compounds used in IV's are an essential part of many cancer patients recovery. If you restrict these compound many cancer patients who have chosen the alternative route will suffer. These compounds really do work and they reduce the symptions caused by chemo as well as aide in the fight against cancer.
Thank your for your consideration.

Dear FDA,

Imagine waking up every morning with the flu. That is what it is like to have Chronic Fatigue Syndrome. I have had Chronic Fatigue Syndrome for the last 11 years. The exhaustion was so pronounced that I was forced to retire from my 20 year professional career at the age of 52. I was later declared totally disabled. I searched every treatment I could find to alleviate the pervasive exhaustion I experienced. One of the treatments I discovered was Methylcobalamin injections. The results were immediate and lasted 2 days for each injection. The Methylcobalamin injections have helped me to function on a daily basis. I have experienced no negative side effects.

Please continue to allow compound pharmacies to provide Methylcobalamin. I and the hundreds of thousands of other current and future Chronic Fatigue Syndrome patients thank you for considering us and our quality of life.

With appreciation,

Methylcobalamin has made a huge difference in my life. My doctor proscribed methylcobalamin after I spent many years feeling constantly fatigued and out of energy. Methylocobalamin has restored my energy and mental clarity. I am now able to keep up with my home and work responsibilities as well as being a much happier person. Please vote to maintain Methylocobalamin as a therapeutic treatment option. Im not sure what I'd do without it.

Thank you

I am writing to ask that "Methylocobalamin remain on the market" for me to buy through compounding pharmacy's.

Methylocobalamin has deeply improved my health.
Taking this medication has:
Stopped painful nephropathy all over my body
Stopped nerve pain in my teeth
Relieved debilitation fatigue
Stopped my hair from falling out
Improved my digestion
Relieved chronic constipation
Relieved depression
Stopped weight gain

It would be a "horrible disservice" to the community to remove this product from the public.

Please do not take this product off the market!!!

Without it being available to me, within 3 weeks to a month I can no longer walk properly without great difficulty. I become so tired that I pretty much become bedridden.

Please keep methylcobalamin available.

I have taken Methycolbalamin since 2012. It was prescribed by my doctor for sciatic nerve pain and energy. It has helped me immensely and has given me relief from the nerve pain and more energy. It has enhanced my life with its therapeutic value. This would negatively affect me should Methylcobalamin be no longer available. I hope that this resource will not be discontinued by the FDA as it has been a great benefit to me.

Sincerely,

Methylcobalamin has changed my life. Within the first 30 minutes after my initial injection, a significant portion of my chronic, daily, debilitating pain was lifted. It is the only thing, in decades of searching, pharmaceutical, herbal, or otherwise, that has made that kind of a difference. If I don't get an injection every 4 days, my pain returns and I am unable to function properly in my work and in my life, which includes caring for my 2 young children. Methylcobalamin keeps me from reaching for opioids, alcohol, and recreational drugs like cannabis to mitigate my pain. I dislike using any of those others because of the negative side-effects and change in mental state that they cause. Methylcobalamin works better for me than any of them, and it has no negative side-effects or psychoactivity that make me unable to perform my activities of daily living.

My need for Methylcobalamin is due to a genetic deficiency, one which I, unfortunately, passed down in a more serious form to my young daughter. We are currently investigating using Methylcobalamin injections to treat her chronic pain, as well. If we no longer have access to it, I don't know what else to use. I don't believe that opioid use is appropriate for most people, but especially not for an 8 year old child.

Being able to administer these shots at home is also far less expensive for us and for our insurance company than if we had to seek more intensive care, which would be the case if our access to Methylcobalamin was shut off. Methylcobalamin is both the best choice, therapeutically, and the most fiscally responsible choice for us.

I know that we are not alone. There are many people in my community alone who have independently come to the realization that Methylcobalamin is the best choice for them in mitigating chronic pain.

Please don't remove our access to this truly life-changing therapy. As much as I want to be able to function, I also beg you on behalf of my daughter and my suffering community members. Please don't make opioids, alcohol, and recreational drugs our only choices!

It is a life saver for me. I get so weak and lethargic if I don’t take it and so tired that I have a hard time functioning I start dropping everything I can’t think right it’s just I have to have it please don’t take it away from me or I don’t know how I would get through the day or how I would survive I have tried taking pills and supplements they just don’t work the same I do not

digesting properly I guess so I need the shots please please I beg you not to take it away

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Hello - I am a 40 year old female from (b) (6) I have homozygous MTHFR and am severally hampered in my methlyation capabilities. I started taking Methylcobalamin in July of 2017 and it has made a significant difference in my energy. I went for needing to sleep for 10 hours a day to 8, feeling more optimistic in general with more energy. I'm a new mom with a 20 month old and this has made the difference from feeling like I was walking through molasses every day to having energy to play with my little one. FDA, please do NOT remove this very important medication.

For many years I struggled with extreme fatigue and eventually was diagnosed with macrocytic anemia (pernicious anemia), which is treated with injections of Vitamin B-12. Not long after it was discovered that I had celiac disease and that my ability to absorb B-12 from my gut was seriously inhibited necessitating lifelong injections to manage my condition. I also have a variant of the MTHFR gene which affects the methylation process. Because of that I must use the methylcobalamin form of B-12 instead of the cyanocobalamin that is offered through mainstream pharmacies, in order to avoid toxicity. Without access to compounding pharmacies--at this point the only source of methylcobalamin for injection--I would still be ill. Because this medication is available to me, I've been able to live a normal life. I genuinely beseech you to recognize the need for this life-changing medication and to allow compounding pharmacies to provide it so that I, and others like me, can be healthy, contributing members of society.

With appreciation for your consideration,

Methylcobalamin has been an absolute life saver for me in dealing with peripheral neuropathy. I experience this problem in my feet, legs and hands. It becomes extremely painful and the methylcobalamin makes my life tolerable. I cannot envision how I'd deal with the neuropathy without it. I've never experienced sides effects from it during the 5 or more years I've used it.
Please consider how important access to this form of vitamin B-12 is to many people in helping with such painful problems.

Sincerely,

I had bariatric surgery several years ago and have been taking vitamin B12 subcutaneously monthly since that time. I never noticed a difference in my energy level or desire to do much for the last several years. Late last year, Dr. (b) (6) of the (b) (6) suggested Methlcobalamin instead of the regular vitamin b12 that I was using. I have been using .1 ml twice a week and have noticed a significant positive change since starting this product.

I hope this product doesn't get taken off the market, I really don't know if anything else will work and I cannot go back to feeling like I was.

Sincerely,

Methylcobalamin injections have been VITAL to my health and well-being. They make a bigger difference than almost anything - and I've tried most everything. Please continue to allow access to this safe and helpful substance.

Thank you for your time.

I, **********, am alive today due to Methylcobalamin, the best form of B-12. For 40 years, I was the picture of health. I lettered in three sports in high school -- Cross Country, Wrestling, and Track & Field. I was also a model student, earning BS Mathematics, MS Mathematics, and (b) (6) MBA. I have taught college students and college graduates for almost 20 years now. I have also been an Actuary.

I continued to exercise 5 or 6 days a week for 22 more years until after my 40th birthday when, in mid-2011, my body would no longer allow me to do so. I experienced such extreme fatigue that I went from kickboxing and Jiu-Jitsu 4 days a week to none at all. I went from running 3 days a week, 2-3 miles a run to warm-up for kickboxing, to none at all. I went from lifting weights 2 days a week to none at all. On (b) (6) 2011, I felt as if I was experiencing a heart attack. My heart hurt -- like it was being squeezed tightly. I was rushed by ambulance to (b) (6) Doctors took myriad tests but could not identify the source of the false alarm. For months, from (b) (6) 2011 through February 2012, I searched and searched for a physician who could determine what was causing my onset of Neurological symptoms: an overloaded central nervous system, an inability to handle even light exercise, brain fog, violent thoughts, dizziness, lack of balance, hands/fingers locking, heart palpitations, etc. I told every doctor that I had long exercised vigorously and that I had from years been a vegetarian (I love animals so I didn't want to eat animals).

The Neurology department at (b) (6) incorrectly identified me as suffering from Carpal Tunnel Syndrome. An ER doctor in (b) (6) falsely accused me of making my symptoms up. Doctor after doctor couldn't get it right until I met the most popular and overworked doctor at (b) (6) (b) (6) who identified that I was suffering from very low B-12. He incorrectly thought that Cyanocobalamin would fix my low Cobalamin. He was incorrect as many of my symptoms persisted despite Cyanocobalamin. Only upon being referred to Dr. (b) (6) in (b) (6) did I receive Methylcobalamin, which passes through the blood-brain barrier and limits my symptoms.
The reason that I had to see almost 20 physicians before being correctly identified as B-12 deficient is that the United States allows a very wide B-12 reference range, with B-12 blood serum test results as low as 200 still in the so-called Normal range. In contrast, Japan uses a minimum B-12 blood serum result of 500 as its low end of Normal. I lived with low and falling B-12 for years and doctor after doctor failed me. Only Methylcobalamin has allowed me to resume a normal life.

I strongly encourage you to not only continue the formulation of Methylcobalamin, but to broadcast to US physicians that B-12 deficiency is the most common vitamin deficiency in the US and that hard-core cases like mine that go untreated can only be fixed with Methylcobalamin. I take Methylcobalamin to this day.

Sincerely,

The use of Methylcobalamin is extremely important to my health. Without it I suffer from extraordinary fatigue. That certainly impedes my ability to accomplish many tasks and reduces my overall enjoyment of life.

Methylcobalamin has been an integral part of my recovery
Please, keep the best interest of patients in mind, and keep it available for us!

Thanks

For several years I've been using Methylcobalamin to supplement my vitamin B-12 absorption. By eliminating my access to this medication will impact my health. Please allow its sale through my naturepathic physician.

I have been self-injecting Methylcobalamin three times a week for several years. It has given me energy! My body has suffered the ravages of tick infection/s and this is just one of the things that I can easily do to have a better quality of life.
Sincerely,

I am dealing with myeloma a bone marrow cancer. When I started taking B 12 Methylcobalamin, my blood cell count improved dramatically. Do not eliminate this product is I depend on it for my survival.
Thank you,

I have been using Methylcobalamin to combat the fatigue of Lyme disease for about 10 years. Weekly injections make all the difference between being physically independent or using a cane. Before finding Methylcobalamin, I was fast heading towards needing a wheelchair. It is my “magic potion.“ I would not want to be without the help in dealing with my disease that it has provided me! Please continue to make this important medication available to those of us who are so helped by it, in our medical conditions!
Sincerely,

Please don't deny my access to the medicinal use of Methylcobalamin by discontinuing it's formulation by compounding pharmacies.

I use Methylcobalamin 2-3 times per week to help support my body so that I am able to go about my daily activities to support myself, physically and monetarily. Methylcobalamin helps me by increasing my energy as well as decreasing the achy-ness that I get through out my body when I don't use it regularly. I have gone without my weekly shots of Methylcobalamin on several occasions and I really, really don't want to have to do that again any time soon!

I am also a health care practitioner. I have heard from a number of my clients how helpful their shots of Methylcobalamin can be in helping them to function in today's world.

Please know that there many individuals that would be effected by a negative decision regarding the formulation of Methylcobalamin.

Warm Regards,

I am responding to the message about why I want to be able to continue my perception of this medicine.
I have been using Methylcobalamin for 3 years. I was having severe pains in my legs, spine and heart palpitations. I went to my Naturpath doctor after several other physicians who couldn't give me an answer for my condition. I asked to be referred to (b) (6) in (b) (6) for further testing. She agreed that was a great idea but first she wanted to do some blood tests and exrays. Everything came back normal except I had very low levels of B12. She gave me a B12 injection. Within a day my pains started to diminish. I was given a prescription and my symptoms continued to improve.

A year later we moved to another state and I stopped taking the B12 injections. The symptoms returned, plus fibromyalgia. I found a Naturpath in my area and after an appointment got a B12 shot and by the next day felt better. I would suffer needlessly if I had to stop taking B12.

My life was totally changed when I started using Methylcobalamin. I went from an unhealthy, under active person to someone with normal energy. Please allow Methylcobalamin to continue to be formulated by compounding pharmacies so I can continue to live in good health.

Methylcobalamin as prescribed by my doctor, is lifesaving to me! PLEASE do NOT take this life-saving vitamin injection away from us! As it is, we can no longer get the higher doses as that has been banned for no real apparent reason and now the FDA wants to further ban a substance that is safe for people. It seems like everything that works which is NOT a prescription is now in jeopardy of being removed by the FDA under the false pretense that it will harm patients! This was done to the intravenous Vitamin C, it has been done to patches and now Methycobalamin is under attack! How many people have died from it? PLEASE just once, listen to the patients that need this injection, made by a compounding pharmacy and save it from being banned by the FDA and turning the United States into a medical tyranny! I do NOT want to see this medication mass produced by a big pharmaceutical company! That will destroy its efficacy by tainting it with preservatives and other chemicals. Not everyone can take prescription drugs due to their extreme side effects! But this vitamin has literally ZERO side effects and works! This is SUPER upsetting! Please do the right thing and leave Methylcobalamin alone!

Thank you for your time,

My name is (b) (6) and I am 68 years old. Twenty years ago my health was going downhill. Unexpected weight gain, muscle weakness and depression. I saw several MD's and I changed my diet and exercised but only saw a little relief. I was told I should have a DNA test. It revealed that because of genetic mutations my body was unable to convert B12 to the usable Methyl B12. I took oral Methyl B12 and got no results. But once I started Methyl B12 shots the results were awesome. I no longer have muscle weakness or suffer from depression. I do not want to think about going back to the way I felt before these shots. My health was so bad my husband didn't think I would live much longer. These shots are life changing for so many of us who have out of the box conditions.

I can't imagine what my life would be like without them.

Thank You,

I have had multiple sclerosis for apprx. 25 years and since METHYLCOBALAMIN is the only one in the B-12 family that can cross the blood brain barrier
it has been invaluable for me in my daily fight to slow down decease progression. Thanks to my daily 5,000mcg daily METHYLCOBALAMIN injection it's the only reason I'm still being able to walk a few steps, have some energy, and many other benefits.

Thank You,

Methylcobalamin has made a huge difference in my quality of life. I have struggled for years with energy levels and it had gotten so severe I was feeling completely depleted and exhausted to the point where it is hard to even put into words. I was having trouble having enough energy to work and was spending just about all of my "free time" resting and trying to recharge just so I could drag myself through another work week, then try to do it all over again. My doctor recommended methylcobalamin and it has made a huge difference. My energy levels are so much better, I am no longer completely stressed out, wondering how I can possibly keep my job when I am so exhausted all of the time and am also able to do more during my free time.

I don't even want to think about what it would be like if methylcobalamin were no longer available. I am finally able to participate in my life again and feel like a human being rather than an exhausted rag doll. I implore you not to eliminate access to this medicine which has drastically improved my quality of life just when I was beginning to lose hope that anything could.

I've lived with a chronic auto-immune disorder for over 30 years. I have learned a lot about how to take care of and support this body so that my quality of life is the best possible, in spite of the disabilities I experience. One of the important additions to my program has been IM methylcobalamin. I've used it for several years as prescribed by my doctor, and feel it would be very detrimental to my well-being if access to compounded, preservative-free methylcobalamin was curtailed. It supports a great many basic metabolic processes in the body that have been impacted by my illness. I know others with chronic conditions that would also suffer if we lose access to methylcobalamin.

Please don't take away one of the medications that improves my quality of life.

Methylcobalamin has helped with my energy levels (chronic fatigue), muscle weakness, depression, and immune function. My absorption of vitamin B12 through food has been compromised due to a bacterial infection in my small intestine I've battled for years. Taking away access to this compounded drug would be detrimental to my health and the health of many others. Please take this into important consideration and do the right thing.

My name is (b) (6) I have a genetic defect known as MTHFR, which means I do not process regular B12 properly. I have suffered for decades (I am 61 now) with extreme fatigue and nervous system issues. A year and a half ago I was finally diagnosed with MTHFR by a Functional Medicine doctor, and put on Methylcobalamin shots weekly. Since then, I have much more energy and am functioning better as a result. The change has been miraculous for me. Recently, my son was also put on methylcobalamin shots (he is 34, mildly autistic and suffers with depression). He is inherited my genetic MTHFR defect. We are seeing improvement in him just 4 weeks on the shots. Please do not take our ability to get Methylcobalamin! We suffered long enough getting answers and deserve better!

Methylcobalamin has been instrumental in helping me overcome a myriad of health issues that came to a fore in late 2016. Unexplained neuropathies in my arms and legs, crushing fatigue, and breathlessness (among other symptoms) were rendering me unable to deal with my everyday responsibilities as a wife and as a mother to two school-age children. Suddenly, I couldn't cook, do laundry, clean, or drive. I could no longer volunteer in my first grader's classroom; I couldn't take my son to swim

lessons. My husband had to take nine months off of work in order to take care of me, our children and our home. My decline was rapid, and very very frightening.
I saw my general practitioner, a cardiologist, a gastroenterologist, a physical therapist, and a neurologist. None of these fine professionals had real answers as to what was happening to me; most could only offer me potent pain medications that I had no interest in taking. Otherwise, I was told, there was nothing they could do.

By luck or grace, after a year of worsening health, I discovered methylcobalamin. When I experienced mild improvement from oral methylcobalamin supplements, I moved to try weekly injections. These gave me more substantial improvement, but the gains wore off a few days after each injection.

Daily methylcobalamin injections have started giving me my life back. Within five weeks of initiating a treatment of 1 mg/mL IM per day, I could finally drive my kids to school again. Within two months, I was doing simple chores around the house. As I write this, I have been on daily injections for five months, and I can now cook, do small shopping errands, take my daughter to dance, and attend functions with my son's Cub Scout troop. I can be a mother and wife again.

I understand the duties of the FDA to protect consumers from potential harms, and I understand that the pharmacological world is a complicated one. But the thought that a committee of strangers might--in the interest of protecting me--take away the very thing that has brought hope and health back into my life.... well, it's a terrifying one. Please keep methylcobalamin accessible to patients like me, who depend upon this simple nutrient to live a normal, healthful life.

I'd like to share a few of the many benefits I've experienced from using Methylcobalamin.
I have Rheumatoid Arthritis and for years suffered from chronic fatigue. The fatigue was so bad that it was difficult to do everyday tasks like caring for my home and working a full time job. I would find myself needing more and more sleep just to get through the day. Even after getting more sleep I still felt tired all the time. The quality of my sleep was poor, I suffered from brain fog (poor cognitive function), decreased awareness and increased bouts of depression.
Since taking Methylcobalamin I sleep better, my mood has improved and I'm more alert. I give myself a shot once a week and if I forget I notice it right away, emotionally, mentally and physically. My joints hurt less and my overall health is better using this drug.

Please don't take this medication away from me, it provides me with a measure of health I haven't experienced in a long time, a feeling of normal.

I've tried this drug in tablet form, over the counter, but it didn't work as well as the shots I get from my Pharmacy.

My life would be negatively impacted if I couldn't continue taking this medication.

I have been taking Methylcobalamin injections weekly almost consistently since 1995. My service in Vietnam in 1968 & 1969 with daily exposure to Agent Orange and 150 mg Benedryl to counter the effects flying daily in combat and combat support. Extreme allergies thru the 70's and 80's led to many doctors until Dr (b) (6) cleared im body of many heavy metals on three occasions in the 90's. Since the 90's, I have been taking 5 shots weekly, including Methylcobalamin.

The above statement is made for justification in support of Compounding Pharmacies to continue support of the practice of providing Methylcobalamin.

Please CONTINUE availability of Methylcobalamin, which is crucial to so many of us for:
Absorption of B Vitamins
Improve moods; less irritability and anxiety; feeling calmer and happier
better digestion
decreased inflammation
diminished headaches
diminished brain fog
Respectfully,

I, (b) (6) take injectable Methylcobalamin due to the inability to absorb b12 because of my INTESTINAL DISEASE!

It has changed the quality of my life, and energy level. Furthermore, because I can only absorb this injectable form, not the oral, it has subsequently greatly reduced my homosysteine levels. Lower homosysteine levels have been associated with reduced chance of heart attack or stoke. (Both run in my family).

It is imperative for my health to be able to continue to be able to obtain this much needed vitamin in injectable form.

This is not a drug or opiate. Why in the world would the FDA involve themselves in trying to make this beneficial vitamin unavailable to people like me??? It is not a drug one could abuse or be addicted to!

PLEASE, do not take away our ability to keep ourselves healthy.

Sincerely,

I am using Methylcobalamin for my pernicious anemia. This is the best thing available for my health. I am a stage 4 cancer patient for the last 6 years, (my life expectancy was only 2 1\2 years) and I need to do everything I can to stay as healthy as I can. If is not available to me I fear that the alternative would be detrimental to my overall health. I can not let my system become weeked by anything. Please make sure that Methylcobalamin continues to be available to me and anyone else that needs it.

Please think of what would you want for your family member if they were in my shoes.

Thank you,

I have been a user of methylcobalamin for more than 20 years. I suffer from Myoclonic jerks. When I use methylcobalamin regularly, my jerking is more controllable. I have been prescribed Methylcobalamin by Mds & Nds from (b) (6) to (b) (6) If these numerous trained doctors prescribe Methylocobalamin to help control my jerking, and I can see and feel the difference in my body, I am convinced that my life is made easier by my use of methylocobalamin. When I don't regularly use Methylocobalamin, my seizures are more frequent and more dramatic. Please do not restrict my access to methylocobalamin.

Thank you.

I have been taking 5mg injections twice a week for three years. It has made a significant difference in my health and life. We experimented with stopping the injections at the one year point and the changes were obvious so I restarted the therapy. Please keep this compound available for us that depend on it to keep our B12 levels up to acceptable levels. Prior efforts to get the same affect from the tablet form have not been as effective.

Thank you,

I am writing about my gorgeous 11 years old female toy poodle, (b) (6) After recovery from some major health issues, (b) (6) was extremely lethargic and would not move from her spot even when called at meal times. I had to pick her up and carry her to her bed in the kitchen to get her to eat. I consulted with two veterinary specialists Dr. (b) (6) in (b) (6) at (b) (6) and Dr. (b) (6) in (b) (6)

I was instructed to do a series of lab work and with the results it was discovered that (b) (6) cobalamin levels were extremely low since her small intestine was not absorbing vitamin b through her food. It was recommend that I give her injections of 25cc of B12 on a weekly basis for four weeks then have her retested. Since (b) (6) has a history of adverse reactions to certain medications and/or treatments, Cyanocobalamin- which has been known to have numerous side effect- was NOT an option. Also, because of the small dosage prescribed, I was only able to fill her Methylcobalamin prescription at a compounding pharmacy.
After a couple of weeks, I saw (b) (6) become more energetic, curious and even playful. I knew that the treatment was working and after four weeks her lab results showed her cobalamin levels had indeed increased. I continue to give her an injection once a month and she continues to do well.

(b) (6) is a family member and her well-being is one of the most important things in our family's life. Being able to access Methylcobalamin at a compounding pharmacy was crucial in (b) (6) recovery as well as maintaining her current quality of life. It has saved my toy poodle from dangerously low levels of vitamin b which she could not absorb through her normal diet.

Please DO NOT take away our right and her right to access Methylcobalamin as a treatment at a compounding pharmacy. If this option is taken away, (b) (6) health and well-being will be jeopardized.

Sincerely,

I am writing to say how methylcobalamin has helped reverse my depression like nothing else. We must keep this an option for those like me that want a full life.
Thank you,

My body does not absorb B12 from food or over-the-counter supplements. As a consequence of this abnormality, I must take methylcobalamin by injection. The Methyl derivative of Cobalamin is the natural occurring form and is far better absorbed than the cyano-derivative. Without methylcobalamin I would become anemic within a very short period of time--in the past I became anemic within 3 months. To have to go to a physician for injections would be very expensive! I also travel extensively and, on long trips, being able to bring Methylcobalamin with me is very important.

My body doesn't absorb B vitamins which will result in death without injections. Methylcobalamin is the only formula that is helping me!

I'm not a Doctor and don't know all the reasons BUT i do know that I feel that this is the only injection that has worked and keeps me going. I'm praying that you please don't take it away!

Thank You

My body is unable to process Methylcobalamin except through inter muscular injection. I have suffered from the results of undiagnosed and untreated Lyme disease for nine years now. The fatigue from this condition is crushing. It is necessary for me to supplement things like vitamin B 12 and vitamin D three in order to try to continue to function rather than sit in a chair. Please do not take away one of the supplements that helps me to function on a daily basis. I need all the help I can get. This disease is devastating. Please continue to allow the compounding vitamin B 12! It is so necessary for so many of us. It is difficult enough to deal with this disease, to have to beg The FDA not to take away supplements that help me is cruel.
Sincerely,

My son ****** was diagnosed with autism at the age of 2 and a half. For me it was crushing and I was on a search for things to better his life. What I read on methylcobalamin spiked my interest. He started the medication at 3 years old. My son has been on Methylcobalamin for almost 4 years. From the very first injection it has greatly increased his awareness and has given him a way better quality of life. Before he was so withdrawn and did not show interest in his brothers or I. Once he started the medication he started talking and started interacting way more with his brothers and I. I stopped the medication once two years ago and he quickly started reverting back to being in social. ****** is a mainstreamed second grader. He would not be where he is today without this medication. It has helped his focus so much. Just recently because of (b) (6) law his dosage was changed and he had a horrible time sitting in his seat or paying attention to the teacher. His teacher called several times asking about medication. Now I could only imagine how horrible his school life would be with no medication. I pray that you guys really are discussing this matter and take into consideration the negative effects it will have on so many if take away. Please realize this is such an amazing medication that truly helps families and improves the quality of life for those who are on it. Thank you so much for your time.

I take methylcobalamin injections every other day. I want to testify to the necessity of continued access to this important treatment. I am a two-time cancer survivor. I was diagnosed with breast cancer in 2006 and advanced colon cancer in 2008. My ileocecal valve was removed in the colon cancer surgery. Until being able to get B12 injections, I was suffering very much from low B12, since B12 is absorbed by the ileocecal valve. I need those injections! Please do not take away my ability to get methylcobalamin. I need it very much!
Sincerely,

I need to have the methlycobalamin product in combination with B-complex injectable for malabsorption issues. Without this drug I have decreased energy levels that are debilitating. I could not work at a full time job without these drugs and would likely have to quit working at my current position that demands a high level of mental clarity and physical activity. As I age this regimen is more critical to maintain a good quality of life.
Sincerely,

Having access to Methylcobalamin has enabled me to continue to be effective in my work. I am a leader in transportation infrastructure and have a position that requires energy to deliver large projects. Traveling to my Dr and making appointments is time intensive. Having home access to Methylcobalamin has meant I can stay healthy and productive.

I take methylcobalamin injections every other day. I want to testify to the necessity of continued access to this important treatment. I am a two-time cancer survivor. I was diagnosed with breast cancer in 2006 and advanced colon cancer in 2008. My ileocecal valve was removed in the colon cancer surgery. Until being able to get B12 injections, I was suffering very much from low B12, since B12 is absorbed by the ileocecal valve. I need those injections! Please do not take away my ability to get methylcobalamin. I need it very much!

Sincerely,

After years of misdiagnoses, my new integrated medical doctor prescribed daily injections of methylcobalamin which has miraculously changed my daily life for the better. One of the most incredible benefits for me was the energy throughout the day. Instead of crashing energywise from early afternoon until a very early bedtime, I can enjoy afternoons and evenings and a pleasant night of sleep. I would never have dreamed this could happen with the methylcobalamin injections as I was taking oral and sublingual B12 tablets which were not working...This Vitamin B12 injection has literally changed my life. I am so grateful and thankful. Please understand how important and critical this is to the quality of my life.

Thank you so very much McGuff Pharmacy and superlative Staff.

Sincerely,

To Whom It May Concern:

It has been brought to my attention that you are considering having the pharmaceutical companies to stop making METHYLCOBALAMIN, I am writing you to make a plea that you do not do this.
My name is ********* and I have been on Vit B injections since they found out that I did not assimilate B through my stomach. They put me on a less expensive Vit B compound but it always made me feel like my brain was craving more. After further testing my Naturopathic Physician noticed that my blood was not accepting most of the initial Vit B compound and started me on Methylcobalamin. My mind is clearer, it no longer feels that craving, I no longer have anemia and my blood work is great! I will be on this medication until the day I die and I will be turning 70 the (b) (6)

I am sure there are many others out there like me whose doctors have them on the lesser expensive Vitamin B, and they probably don't know that their bodies are sluffing off most of it and need to be on the Methylcobalamin instead.

Doctors will give Vitamin B shots to patients to just give them a lift, but to me it is the life blood for my brain, because without it I become extremely anemic and my brain starts to starve and I start losing memories!

So please, do not stop making METHYLCOBALAMIN, there are still some of us that desperately require this medication. If you need to just raise the price a little, but don't stop making it. I pay for this out of pocket not by insurance.

Thank you.

Hello,

I read a frightening letter concerning the availability of Methylcobalamin. Unfortunately, I have a variety of physical maladies, including anemia, and Methylcobalamin helps to keep iron in my blood and give me energy. Last winter I needed 4 iron IV's because my iron was so low. Currently, I'm on SSDI for a genetic disorder, and have great troubles getting enough energy to do the basics of taking care of myself. Methylcobalamin helps me greatly with vitality. Hearing it might be taken away is terrifying, as I haven't found another source of B-12 that has worked anywhere as well. Please continue to allow me to have access to a medicine I need!

Peace and Abundance,

I had a severe B12 deficiency for at least 17 years before it was correctly diagnosed. As a result I have permanent neurological damage and also, secondarily, damage to joints from falling as a result of the deficiency. Because my damage was mostly neurological, methylcobalamin was selected because it does not have to undergo another step before helping the nerves.
Cyanocobalamin also does not last more than 24 hours in the system and, in regular pharmacies, contains additives that I cannot tolerate. Thus I need methylcobalamin custom compounded.
My need for this compounding is completely for medical/deficiency reasons. I am not injecting it simply because I want more energy, although extreme energy depletion was one of my original and long lasting symptoms.

This is not a dangerous drug! The FDA seems to let more dangerous drugs pass approval than allowing non dangerous substances. Is this not a ploy by the mainstream pharmaceutical industry to gain some financial advantage?!

Sincerely,

I've been using this compound for years. The formula has help with my nerve pain and anxiety/ depression. I prefer not to use harsh chemicals in my body and this has kept me feeling energized and mostly pain free. If I loose the availability of use of this compound , it would be detrimental to my recovery.

I am one of your customers who will be very upset if the FDA takes away our right to purchase methylcobalamin. It is the only source of B-12 my body can assimilate. I have a B-12 deficiency and need it to keep my nerves and body healthy. What do I need to do to protect myself from depletion of B-12. Help!!!

I have many complications with my Crohn's disease, SIBO, and small bowel obstruction. I rely on B12 injections once a week to help me maintain strength and wellness.
Methylcobalamin, has been a life saver for me to have available access through compounding pharmacy such as McGuff Pharmacy.

Please do not make this so inaccessible to our public.

Thank you,

To Whom It May Concern,

I would like to strongly advocate for the continued availability of Methylcobalamin as a viable treatment option for those populations that benefit from it's therapeutic value. I have had anecdotal discussions with individuals who feel the methylated vitamins have dramatically improved their quality of life, including improved mood, lessened anxiety / irritability, decreased inflammation, clearer thinking, and a increased sense of calm and happiness. Further, they report improvements in their digestive health and decreased headaches.

I have also seen some promising data that points to Methylcobalamin as a potential analgesic, which is promising, and I understand it's application in the role of treating Alzheimer's and Rheumatoid Arthritis, which are conditions I have seen my grandmother and father struggle with, respectively. As a provider of Substance Abuse treatment amidst the growing opioid epidemic, I welcome all forms of holistic, preventative alternatives to managing pain as opposed to narcotics.

Respectfully,

I suffer malabsorption of vitamin B-12 which is Methylcobalamin due to a chronic Gastro-intestinal issue. Vitamin B-12 is not able to absorb well orally in my system. The only way to achieve a normal B-12 level is by injectable Methylcobalamin. Not having injectable B-12 would negatively impact my health. I have heard that I need Vitamin B-12 shots from both a (b) (6) doctor and another doctor as well. I want to continue to be able to access Methylcobalamin for my health in the future.

Sincerely,

To Whom It May Concern:
I have been using compounded Methylcobalamin for many years. While in the course of being diagnosed with Parkinson's Disease, I was also diagnosed with B12 deficiency. I started on oral doses, but as a person with Parkinson's (PWP), my swallowing has become compromised (as is common with PWP) and the compounded injection is a much better delivery method. Without access to it I will be forced to take it orally which puts me at a higher risk for choking or aspirating it. Please do not restrict access to this very beneficial and necessary prescription.

Sincerely,

Hello,
I am writing for me and my 3 sons. Between the four of us the ability to inject compounded methylcobalamin has given us life back in many ways. My ability to absorb B vitamins dictates me taking both oral and injected methylated forms. I have improved moods, less irritability and anxiety, no numbness in toes and finger tips, better digestive health, decreased inflammation throughout my body, lessening of headaches , less foggy brain and I feel much calmer and happier. My son's are similar. Please help us.

I [XX] have been very successfully using prescription injectable methylcobalamin for 19 years to treat pernicious anemia/atrophic gastritis. I cannot absorb oral B-12 and do not do as well with other forms of injectable B-12 because of methylation issues.
Please tell the FDA not to make any changes that will endanger my health and well being that has taken much time and much suffering to achieve.

I do not want to stop using injectable Methylcobalamin because that would jeopardize my health and put me at risk.

I am concerned very much with the FDA restricting the access to Methylcobalamin ie B12.I have had Parkinson's disease for 5 years and this solution is very important to my well being. The injection method increases my activity level and feeling of well being that can not be achieved with tablets.

Please consider my plight.

Sincerely

To whom it may concern,
We have been using compounded injectable Methylcobalamin for two years now & we have noticed a marked improvement in our health. One being that we haven't gotten a cold or flu as many around us have. We also have noticed that it has benefited us with stress levels as well as seems to have improved our sleep.
We feel that it is very important to continue to have this available to those of us who want to take care of ourselves in a preventative way.
Best regards,

To Whom It may Concern:
I have been using methylcobalamin since about 2002. At that time i was diagnosed with achlorhydria-a lack of stomach acid, which i don't expect to ever be resolved. Since the cells that manufacture the hydrochloric acid of the stomach also manufacture the attachment protein for Vitamin B12 the chance i could ever absorb B12 in the gastrointestinal tract are nil. I need that methylcobalamin as an injection to survive. I do not tolerate cyanocobalamin. If you prevent pharmacies from compounding methylcobalamin, you are signing my death warrant.
Sincerely,

Hi,
Thanks for reaching out. Please fee free to use me as a reference for keeping the methlycobalamin available for purchase through your pharmacy. This vitamin injection has helped me to have more energy, relieve some depression and anxiety and increase my digestion. It would be determinantal to my health to not be able to have this available to me.

To whom it may concern,
I have been a Methylcobalamin user for 3 years.
My doctor prescribed this medication when I was starting menopause. I was unable to function my day to day life until I started taking this medication. It helps my immune system stay strong and fight illness. It gives me the energy to live my life to the fullest. Without this medication, I'm afraid my immune system will fail. Please continue to allow me to purchase this medication under the care of my doctor.
Thank you,

I am strongly advocating the continued use and availability of methylcobalamin for use in treating health issues and improving quality of life.
Please allow the compounding pharmacies to continue to compound methylcobalamin so that those of use who need it and benefit from it, can continue to have access to it and enjoy a much healthier and more productive life.

I am a client and a patient who is dependent on having regular access to Methylcobalamin shuts for my health treatment. My doctor regularly prescribes it for me and the thought of not having access to methylcobalamin is very upsetting and concerning for me . Please continue to make

methylcobalamin available and accessible so I can continue to receive the treatment I need.

To whom it may concern,

I am strongly advocating for the continued use and availability of Methylcobalamin.
For me personally, I spent decades trying to figure out the combinations of symptoms of anxiety, depression, inflammation, cardiac issues, digestive issues, low energy and foggy thinking. Finding a combination of health & genetic issues that can successfully be treated by methylcobalamin literally gave me my life back. For me it is as essential as insulin is to a diabetic. I am a different person on methylcobalamin,more functional and fully able to contribute to society. My moods are improved, my thinking is clearer, my energy is significantly better, and I have an increased sense of calm and happiness. It has dramatically improved my health and the quality of my life.

I obtain methylcobalamin through a physician's prescription from a compounding pharmacy. I don't know what my alternatives will be if those pharmacy cease to be able to produce it.
Please allow the compounding pharmacies to continue
to compound methycobalamin so that those of use who need it and benefit from it can continue to have a healthy and productive life.

Respectfully,

A few months ago I wanted to go off injectable methycobalamin to decrease my expenditure and for convenience. I took large doses of oral methylcobalamin (1000-2000mcg) during the week or two I was off the injectables. It was clear in just those couple of weeks that my body was not getting or assimilating enough. When I went back on the injectables my energy and mental focus returned and improved. I believe the methyl form of cobalamin is the most active form and what my body, and many others, need. I would not feel well if I did not have this form of methylcobalamin.

I have been on Methylcobalamin for about a year. I started with trail for depression. I was on it for 2 weeks and feeling very much better .... less sadness and fewer episodes of crying. After the trial I was off it for about 2 weeks waiting for my prescription.
During his time my depression worsened with increased sadness and multiple bouts of crying daily again.

This has been very helpful for me and improved my quality of life greatly.
I am writing it to the FDA in behalf of my family and all of the families that have genetic disorders such as MTHFR , absorption issues, and pernicious anemia ... that so desperately need Methylcobalamin, to lessen the effects of anxiety, depression, digestive disorders, cardiac issues, low energy, dementia and nerve damage.

Hello,

Just a little over 2 years back, I was suffering from Hashimoto's disease. I was extremely anemic (with a ferritin of 4), b12 DEFICIENT, and severely iodine deficient. Thanks to correcting iodine deficiency, I am no longer testing positive for Hashimoto's and haven't for almost two years now. I am still currently fighting two different types of parasites. Based on symptomology, I

have likely been battling at least one of these parasites for eleven years, despite the fact that I am only 27 now. Before I was able to inject methylcobalamin at home myself, I had numb feet and hands; indeed, the sensation of pins and needles was extreme enough that I sometimes was unable to stand on my own two legs after sitting for more than 4 minutes. I couldn't walk without my heart going through the roof and becoming very short of breath. I used to have daily nausea, low blood pressure, and my heart barely beat at 51 pbm. I felt completely out of it.

I am a very athletic, in-shape individual. This was never about being lazy. I swam in college and had these symptoms from the age of 16 to the onset of injecting methylcobalamin at home. My life is so much better now; indeed, my moods are even and I no longer have either brain fog or tinnitus and I do not black out whenever I stand from a seated position. I used to suffer from heart palpitations and I couldn't function for the 4 hours after waking in the morning. My morning nausea is gone. All of this changed once I was able to give myself b12 shots. I WAS taking a b12 supplement orally when I found out (via lab tests) that I could NOT absorb it due to my parasite issues. This will not change until my parasites are gone. I need to be able to inject methylcobalamin myself. The synthetic form of b12, cyanocobalamin, will not work for me either. While some individuals just view b12 as an "energy shot," it is MUCH more to some of us. It is the difference between enjoying life and having a miserable existence. I do not relish the idea of having to go to a doctor's office to receive b12 shots EVERY WEEK, TWICE A WEEK. That's how often I need them. I have had them done in-office before, and the needles are far too long and leave a bruise on my rear that will not go away. Plus, this constant need for shots will only clog up doctor's offices even more. Who has the time for this? I know that I, for one, do not.

Thank you and I hope that this information helps shed light on just how important methylcobalamin is to a LOT of people and why it needs to remain accessible to patients

One of the side of effects of our sons autism has been OCD and Methylcobalamin has been an incredible help controlling his OCD. If he goes too many days without an injection, his OCD starts acting up. I don't know what we would do without it.
Please pass along to the powers that be that I NEED Methylcobalamin!! I carry the MTHFR genetic inability to metabolize B vitamins. I have been self administering Methylcobalamin for approximately ten months now and it has changed my life. I can’t imagine how I will be able to function again without it. Please, do not interrupt my ability to work and to function.

The idea that I may not be able receive Methylcobalamin is devastating. I can not go back to the levels of exhaustion and the limitations I experienced.

Q. Please provide any additional information that FDA should consider in its evaluation that may help to clarify the role of the nominated methylcobalamin bulk substance in compounded drugs products in current clinical practice, such as statements or guidelines from professional medical societies.

A. Professionals’ Statements:

Dear Committee members:
I understand you are asking for additional information to defend why these following ingredients should be reviewed and included in the 503A bulk drug substances list:

- Methylcobalamin
- Quercetin

- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

I have been using these agents safely and successfully for many years and I would like to urge you to include these substances in the 503A bulk drug substances list. They are extremely valuable and I would like to share one anecdote that exemplifies this:
On April 25, 2016 I was consulted by a 69 year old woman complaining of pain in her hands and feet of several months duration, with erythema and dry skin, as a result of chemotherapy-induced peripheral neuropathy from Taxotere that she had received for localized inflammatory breast cancer. Two days later she returned to my clinic and received an intravenous infusion of alpha lipoid acid 250 mg and followed by an intramuscular injection of methylcobalamin 5 mg. The following day she reported that her pain, the erythema and dry skin had all completely resolved within the prior 24 hours.

To this day (February 20, 2018), there has been no recurrence of any symptoms of the peripheral neuropathy, and the patient is asymptomatic with minimal residual disease.
This case is just one of many of my patients that have benefitted from the valuable agents in questions. Please use your authority to preserve their availability.
Thank you.

Sincerely,
Michael Traub ND, DHANP, FABNO
Primary Care Medicine
Board Certified in Naturopathic Oncology

Dear FDA PCAC,
I am writing to inform you on the significance and impact injectable methylcobalamin has on my medical practice. The use of injectable methylcobalamin has positively impacted the activities of daily living of many of my patients, whom receive injections for various ailments. The most notable effects have been seen in those suffering from cognitive decline, pain syndromes, anxiety, depression, chronic fatigue, multiple sclerosis, insomnia, general fatigue and chronic migraines.

Some patients had previously been prescribed cyanocobalamin, which in many appeared to have negatively impacted their mood and anxiety anxiety, contributed to headaches and in many instances, had no effect at all. The use of preservative-free injectables is crucial to the overall health and well-being of our chemically sensitive and genetically fragile patients.

Through genetic testing, we have been able to isolate individuals whom are unable to convert cyanocobalamin to the active form of methylcobalamin. If this product becomes unavailable to prescribers, many of my patients will suffer, as chemical-free active B-12 injectables are nonexistent.

Compounding such products is essential to the overall health of many. The efficacy of
oral B-12 does not compare to the efficacy of injectable B-12, as stomach acid, stress, and amount of intrinsic factor produced in the stomach are all factors of absorption of the oral route of B-12. By bypassing the gut, we can ensure that our patients are receiving a therapeutic dose of B-12.

Thank you for your time and consideration.

Sincerely,
Danielle Schwaderer Kettler, ND

Hello,
I am concerned about restricted access to compounded medications. In practice, I have tried to switch patients to other forms of B12, for example, and the results are not as positive as with methylcobalamin. In fact, I have had patients report near magical improvements with active B12 on board in terms of depression alleviation, insomnia relief, and overall energy improvement. Providers need to have these options available so that patients need not suffer with subpar prescriptions that don't address their concerns as elegantly as compounded formulas can.

Best,
Katrina Iiams-Hauser, ND

Hello,
Thank you for taking the time to read about the use of methylcobalamin in clinical practice. I have been using methylcobalamin in my practice for over a year. This compounded vitamin has changed literally hundreds of my patients' lives. I have seen the following:
- reduced anxiety
- improved stress response
- weight loss
- improved sleep
- general mood improvement
- reduced aggression
- improved immune health

All of these benefits have been reported by my patients. Many of these patients had sought out pharmaceuticals to address all of the above conditions without any reprieve. Many patients had sought out cyanocobalamin or hydroxycobalamin injections previously without any benefit. We are seeing an increase in patients with methylation difficulties, and removing methylcobalamin would be incredibly detrimental to their health.
Dosing:
IM: 2.5 mg biweekly
IV: 5 mg monthly

Thank you for your time,

Dr. Elisse Evans, ND
Origins Integrative Medicine

Please CONTINUE the availability of Methylcobalamin to compounding pharmacies, which is crucial to many of my patients for:
-Absorption of B Vitamins
-Improve mood; less irritability and anxiety; feeling calmer and happier
-Better digestion
-Decreased inflammation
-Diminished headaches and brain fog

Respectfully,

Michael Cutler, M.D.

Hello and thank you in advance for your time. I am an NMD, in practice for over 10 years.

In my practice, I use methylcobalamin injectable on a daily basis. There is nothing that works better for macrocytic anemia. Oral B12 or cyano B12 does NOT work when the deficiency is great. I have been practicing for 10 years and have been using this product with success, no adverse reactions, ever. I have helped thousands of people with deficiencies recover quickly with weekly injections, confirming they are better with before and after testing and verbal confirmation. Genetic SNP's, such as MTHFR, MTRR, and MTR make cyanocobalamin a waste of time and money, it also contains a toxin I refuse to use. Methylcobalamin is the answer there.
These medicines are vital to the practice of medicine and should remain available to doctors everywhere.

Respectfully,
Wendy Wells, NMD

I am writing a patient account in support of the compounding of methylcobalamin. I have a patient who has pernicious anemia and genetic mutations affecting her methylation. She has seen improvements since doing injectable cyanocobalamin. However, we changed her injections to methylcobalamin 2 months ago and her energy has been steadily and dramatically improving in a way we have not seen with any other form of injectable cobalamin. She has been able to exercise and is also sleeping better since this change. This has had a profound impact on her daily life, her work, her relationships, and what she feels is possible for her future. Without the methylcobalamin, I have every reason to believe she will lose these improvements since that was the only thing in her treatment that changed to correlate with these improvements.

Kimberly Hindman
Naturopathic Physician, Licensed Acupuncturist

My name is Sarah E. I am a medical assistant for Dr. Wendy Wells. I have seen and heard some great things from our patients after receiving methylcobalamin injections. Many of our patient receive them on a weekly basis and just some of the benefits they have told me about include:
- Increased Energy
- Decreased Appetite
- Decreased Depression
- Brain Fog has decreased
- Better Sleep
- Hair Loss has diminished

I do hope to be able to continue to assist our patients with these benefits, and would like the FDA to take these examples into consideration.

Respectfully,
Sarah Essley
Medical Assistant
15 Years Experience
US Navy Veteran

I have used many of these compounded substances in my practice for a variety of patient specific needs. In fact I have never used as B12 other than methylcobalamin for IM or IV applications as the majority of the American population has an MTHFR SNP I would give the activated form to all patients without adverse events. I have used L-glutathione (L-GSH) IV to support detoxification as this is our bodies most powerful antioxidant, specifically in people who are detoxifying from drug/etoh use and heavy metal/chemical/mold exposures. 1000-2000 mg qwk GSH IV in Parkinson’s disease has improved symptoms regardless if they are using carbidopa-levodopa or other pharmaceuticals to improve symptoms. In addition to IV

GSH I typically add in oral GSH. **PMID: 8938817, 19230029.** I have used IV ALA, choline, and quercetin less frequently, though, with symptomatic improvements and no adverse events.
These compounded substances have been beneficial to numerous patients in my practice. It is important to maintain access for patients to these high quality compounded substances. I'm grateful to McGuff Compounding for providing outstanding service and products for our patients and continuing to stand for compounded substances.

Sincerely,
Audrey Schenewerk, ND, MS

I've been working in the field of integrative mental health since 2011. At that time, we were just learning about genetic mutations related to the methylation cycle (specifically, at that time, the MTHFR mutation) and how they impacted mental health. I provided care primarily to people covered by Medicaid, people who were often unable to work due to disabling anxiety, depression, tics, tremors, and mental health diagnoses such as schizophrenia.

By studying the methylation cycle and the reactions which were limited by various genetic mutations, it was a fairly simple matter to determine what nutrient(s) or cofactors were needed to optimize pathway functioning. In most cases, methylated vitamin B12 was needed in conjunction with methyltetrahydrofolate to improve neurotransmitter function (and provide a great deal of benefit for cardiovascular health and fertility, to name just two other systems affected).

I have used methylcobalamin injections with my patients since 2012 and this has been a life-changing therapy, particularly for people with chronic, debilitating anxiety and depression. I urge you to educate yourselves about genetic methylation defects and keep Me-B12 in the compounding formulary. Individualized medicine based on each person's genome must be the future of medicine, and to pull this cornerstone of treatment would be, in my opinion, a grave mistake.

Sincerely,

Lesley Morical Kuramoto, ND

Methylcobalamin, the safe, effective, activated, methylated form of vitamin B12, is a vital component in my therapeutic regimen for my patients with a wide range of disease conditions, both orally and intravenously, for preventive care and treatment. It must remain available to my patients and I, since it is in the best interests of the public health and welfare.

Sincerely,
Mitchell A. Fleisher, M.D., D.Ht., D.A.B.F.M., Dc.A.B.C.T.
Center for Integrative & Regenerative Medicine

Methylcobalamin is vital to the patients we treat. Dr. Christopher Surek MD. DO is having incredible results with patients with the genetic factor MTHFR. The only thing that works is this B12. Please help us help our patients with this incredible B12. We have helped many patients with low immune systems and chronic pain. Please understand the importance of this B12. Please contact us at 3189412057. We are a very small rural clinic and we try and help those we can. Thank you. God Bless.

Dr. Rose Kuplesky RN, BSN, ND
Dr. Christopher Surek MD, DO

Case study #1
70yo African American Female has been using injectable methylcobalamin for several years to help treat mood dysregulation. The patient also takes a daily oral supplement but when she misses her injection she becomes significantly more aggressive, anxious, and irritable. This has been reported by herself, her primary caretaker, and her son. The patient has been on injections of cyanocobalamin without similar effects and therefore would need to continue on her current regimen to help improve her mood. She is unable to tolerate other medications used to help with mood regulation and is dependent on her injection.

Case Study #2
42yo Caucasian Female with FMH of CAD/MI and renal disease who presented with chronic fatigue and high normal homocysteine with elevated B12 and folate. Patient was on oral supplements of both methylcobalamin and cyanocobalamin with limited response as demonstrated by continued elevation to homocysteine. Patient was placed on weekly injections of methylcobalamin with improvement to both fatigue and homocysteine levels. Patient has not had any cardiac event or renal impairment.

Several patients with MTHFR mutations have responded well to injections of methylcobalamin as they are unable to methylate ingested by-products in vivo. They generally benefit the most utilizing a combination of oral regimen and injections to help minimize risk for cardiac events and neuropathy. They typically present with high homocysteine and high serum vitamin B12 and Folate as they will have used oral OTC products without significant improvement to symptoms or labs.

I truly hope this helps as it would be devastating to our office and patients to no longer have this as an available option.

Thank You,

Ariel Causey, BS, MSN, RN, FNP-C
ReVitalize Health and Wellness Center

Victoria Sucher, ND – see accompanying letter.
Blue Flower Medicine

Dean Mitchell, MD
Ricki Mitchell, MD – see accompany letter.
Mitchell Medical Group of New York

Please let us know if you are in need of any further information.

Sincerely,

Ronald M. McGuff, President/CEO
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., STE 142
Santa Ana, CA 92704

BLUE FLOWER
MEDICINE

February 23, 2018

RE: Methylcobalamin, PCAC Review information

To Whom It May Concern;

We have been treating patients for over 10 years. We treat patients who have digestive issues, methylation defects (patients with documented MTHFR and COMT genetic mutations), chronic illness, infectious diseases, neurological conditions, chronic fatigue, and autoimmune disorders. Many of these patients with the above stated conditions do not tolerate cyanated compounds. They do better with adenylated or methylated nutrients. The cyano groups tend to cause more liver issues or mast cell destabilizing issues in these types of patients, not to mention allergic reactions.

The majority of these patients also have Gastro intestinal issues secondary or primary to their other health concerns. They are not able to break down/methylate the vitamins and nutrients that they are given. In these more severe cases patients do not respond to oral methylcobalamin. They are in desperate need to get their health back on track and being able to use injectable compounded methylcobalamin is a critical part to their treatment plans.

Many patients who have been ill for a number of years have also developed multiple chemical sensitivity. It is crucial to these patients that we have the ability to order and utilize compounded medications in small controlled batches that are free from preservatives and additives. We have had several patients with methylation issues that when given oral or injectable cyanocobalamin they have had adverse effects, when the same patients are given methylcobalamin they do not experience adverse events.

We already have patients suffering because of the limitations and laws recently put on the injectable vitamin c. I have several patients with severe corn allergies and despite what the overall research shows I have personally seen them have reactions to the standard/commercial mixes of injectable vitamins including but not limited to hives, trouble breathing, and rashes. Please allow me to continue to give the best possible care for my patients by allowing the continuation of using compounded vitamins especially Methylcobalamin.

Sincerely,

Victoria Sucher, ND
NPI 1104895069

3620 North University Avenue #200
Provo, Utah 84604

Phone: (801) 852-9899
Fax: (801) 375-7102

MITCHELL MEDICAL GROUP OF NEW YORK, P.C.
Immunology, Alternative and Integrative Medicine

57 WEST 57TH STREET, #601
NEW YORK, NY 10019
TELE: 212-586-7400
FAX: 212-586-6880

165 NORTH VILLAGE AVE, #129
ROCKVILLECENTRE, NY 11570
TELE: 516-678-9600
FAX: 516-678-9618

FACSIMILE TRANSMITTAL SHEET

TO: Pharmacy Answers	FROM: Dr's Dean & Ricki Mitchell
MITCHELL MEDICAL OF NY	DATE: 02/13/2018
FAX NUMBER: 877-444-1155	TOTAL NO. OF PAGES INCLUDING COVER: #1
PHONE NUMBER: 877-444-1133	SENDER'S REFERENCE NUMBER:
	YOUR REFERENCE NUMBER:

X URGENT X FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

ITEMS CONTAINED IN THIS FAX ARE CONFIDENTIAL AND INTENDED FOR PRIVATE USE ONLY

TO WHOM IT MAY CONCERN:

We see many patients with chronic illnesses, in addition to MTHFR defects who require Methylcobalamin. Cyanocobalamin would be ineffective for their conditions.

We write our patients over #100 prescriptions per year for "compounded Methylcobalamin. Thank You.

Tab 2c

FDA Evaluation of Methylcobalamin

DATE: May 11, 2021

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Susan Johnson, Pharm.D., Ph.D.
Clinical Reviewer, Pharmacy Compounding Review Team (PCRT)
Office of Specialty Medicine (OSM), Office of New Drugs (OND)

Wafa Harrouk, Ph.D.
Senior Pharmacology/Toxicology Reviewer, Division of Pharm-Tox, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine; PCRT, OSM, OND

Kemi Asante, Pharm.D., MPH
Consumer Safety Officer, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Science Advisor (acting), ONDP, OPQ

Daiva Shetty, M.D.
Associate Director, PCRT, OSM, OND

Charles Ganley, M.D.
Director, OSM, OND

Frances Gail Bormel, R.Ph., J.D.
Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Methylcobalamin (Methyl B_{12}) for Inclusion on the 503A Bulk Drug Substances List

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

Methylcobalamin was nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This review considers methylcobalamin, also referred to as methyl B_{12} in the nominations, for potential use in treatment of autism spectrum disorder (ASD); amyotrophic lateral sclerosis; various peripheral neuropathies; various pain conditions; hyperhomocysteinemia; various inborn errors of metabolism, including methylene-tetrahydrofolate reductase (MTHFR) polymorphisms and conditions affecting cobalamin absorption and metabolism, and vitamin B_{12} deficiency.

Methylcobalamin products proposed in the nominations are:

- Injectable solution 0.5 to 12.5 mg/ml for subcutaneous or infusion administration
- Oral 500 to 5000 µg
- Sublingual 500 to 5000 µg troche or liquid
- Nasal spray 250 to 500 µg/spray dose of 0.1 mL

The relationship of methylcobalamin to vitamin B_{12} will be explained in subsequent sections of this review. The nomenclature describing the substance that is the subject of referenced information is taken directly from the published material (e.g., "methylcobalamin" or "vitamin B_{12}").

We have evaluated publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing methylcobalamin on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[1]

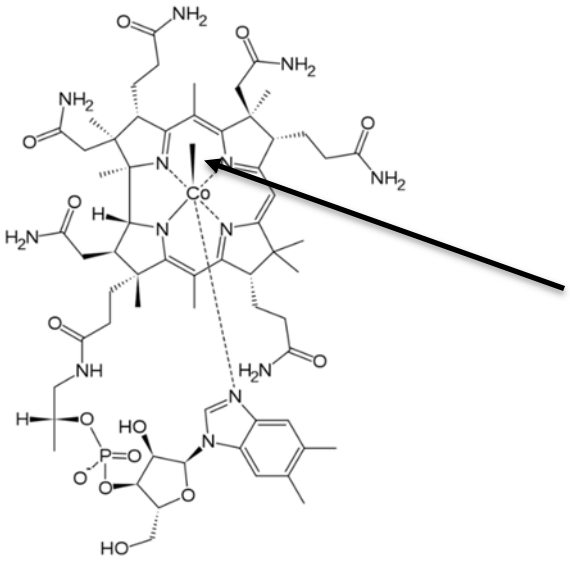
Databases searched for information on methylcobalamin in preparation of this section included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and the United States Pharmacopeia /National Formulary.

Vitamin B_{12}, is a group of 4 substances, or vitamers, that include cyanocobalamin, hydroxocobalamin, adenosylcobalamin, and methylcobalamin. These related molecules are

[1] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

centered on a core cobalamin structure that includes a cobalt ion. Methylcobalamin, the active pharmaceutical ingredient (API) under consideration, has the molecular structure shown in Figure 1. The arrow points to the methyl group that distinguishes methylcobalamin from the other cobalamins: substitutions of different ligands at this site are associated with the other 3 cobalamin molecules.

Figure 1. Methylcobalamin structure (Ganesan et al. 2012)



Ligand changes at this position form different cobalamins:

CH_3, as shown - methylcobalamin

OH – hydroxocobalamin

CN – cyanocobalamin

5' deoxyadenosyl - adenosylcobalamin

Methylcobalamin occurs naturally in foods such as fish, meat, eggs and milk. It is currently marketed as a dietary ingredient in dietary supplements capsules and tablets (1 mg and 5 mg) products. Methylcobalamin has a USP dietary supplement monograph but does not have a USP drug monograph.

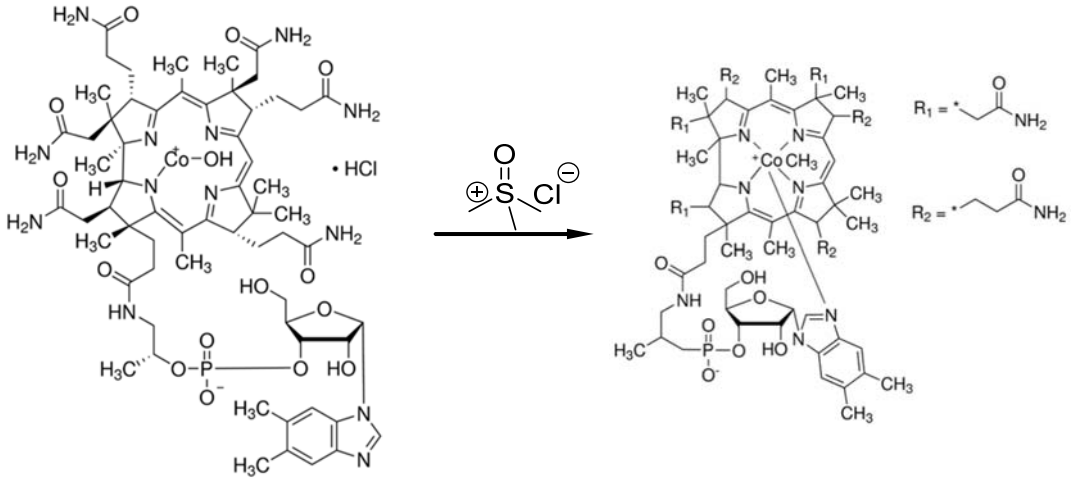
1. Stability of the Active Pharmaceutical Ingredient (API) and likely dosage forms

As a vitamer of cobalamin, methylcobalamin is stable at room temperature, but very photochemically labile. Under neutral conditions, methylcobalamin is converted into hydroxocobalamin within seconds of exposure to ultraviolet light and is then further oxidized (Juzeniene and Nizauskaite 2013). Another study showed that, the aqueous injection solution of methylcobalamin is sufficiently stable under neutral conditions at room temperature as well as under acidic conditions and oxidative conditions (H_2O_2) for 8 hours. However significant degradation was observed under basic conditions or when temperature was raised higher than 50 °C (Ganesan et al. 2012). A study published in 2019 (Ip et al.) showed that methylcobalamin injections can be stored for at least 181 days at room temperature in amber serum vials and protected from light. The decrease of the API concentration did not exceed 10%. Therefore, methylcobalamin is likely to be stable under room temperature in its solid formulations (capsules, tablets, sublingual troche, etc.) when protected from light. Similarly, with protection from light and proper formulation techniques (e.g., controlled pH and temperature) the substance can be stable when compounded as liquid formulations (such as injectables and oral solutions).

2. Probable routes of API synthesis

Synthesis of methylcobalamin is mainly based on the methylation of hydroxocobalamin (see scheme in Figure 2). The methylation reagent involved here is usually trimethylsulfoxonium derivatives (Hisatake et al. 2004).

Figure 2. Methylcobalamin synthesis (Hisatake et al. 2004)



3. Likely impurities[2]

Likely impurities may include:

1) Residual starting materials and reaction intermediates, including hydroxocobalamin;
2) Byproducts from the photochemical degradation of the product, and further oxidation products.

4. Toxicity of likely impurities

The above mentioned impurities are unlikely to be present at a highly toxic level.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Methylcobalamin is a dark red crystalline solid, which is slightly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability was found in the literature.

[2] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. Compounders should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration and chronicity of dosing.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

Methylcobalamin is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Methylcobalamin is a cobalamin vitamer and it is likely to be stable under ordinary storage conditions with protection from light when compounded as solid and liquid formulations. When compounded as aqueous solutions, proper formulation, including controlled pH, controlled temperature, and potentially other measures, may be needed to achieve sufficient stability for the drug substance. Methylcobalamin is easily characterized with various analytical techniques and the preparation of this compound has been well developed.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Embase, Web of Science, ToxNet, NIH dietary supplement label database, Google, GRAS notice inventory, and Drugs@FDA

a. General pharmacology of the drug substance

Methylcobalamin is one of a group of structurally-related molecules, vitamers, of vitamin B_{12}. These are also referred to in the published literature and in this review as "cobalamins." "Cobalamin" is a term used to refer to one of the four cobalamin vitamers or to the central structure, without a ligand. Cobalamins, from dietary or other sources, can be converted through a series of metabolic steps to serve as a coenzyme to cytoplasmic methionine synthase. The enzyme and cofactor participate in methylation of DNA, RNA, and histones, and plays key roles in genetic expression (Green 2017).

Figure 3 is a schematic of oral intake and gastrointestinal absorption of cobalamins (Shipton and Thacihl 2015, Allen et al. 2018). Of note for the purposes of this review:

- Once ingested, cobalamins are disassociated from food proteins in the low pH of the stomach and initially bound to haptocorrin.
- Cobalamins become available to bind with intrinsic factor in the higher pH of the duodenum and ileum.
- A receptor-mediated calcium-dependent endocytosis internalizes the intrinsic factor-cobalamin complex into the ileal enterocyte. The cobalamin is released from intrinsic factor and binds with unsaturated transcobalamin or haptocorrin in the plasma for transport to the liver and other cells.
- Generally, nasal spray and sublingual dosage forms are intended to amplify absorption by taking advantage of the exposure of local vasculature. Methylcobalamin is believed to be absorbed in the nose and mouth by passive absorption, rather than the receptor-mediated mechanism. This likely reduces absorption compared to oral dosage forms that are intended to be immediately swallowed.

Figure 3. Cobalamin absorption (Shipton and Thacihl 2015)

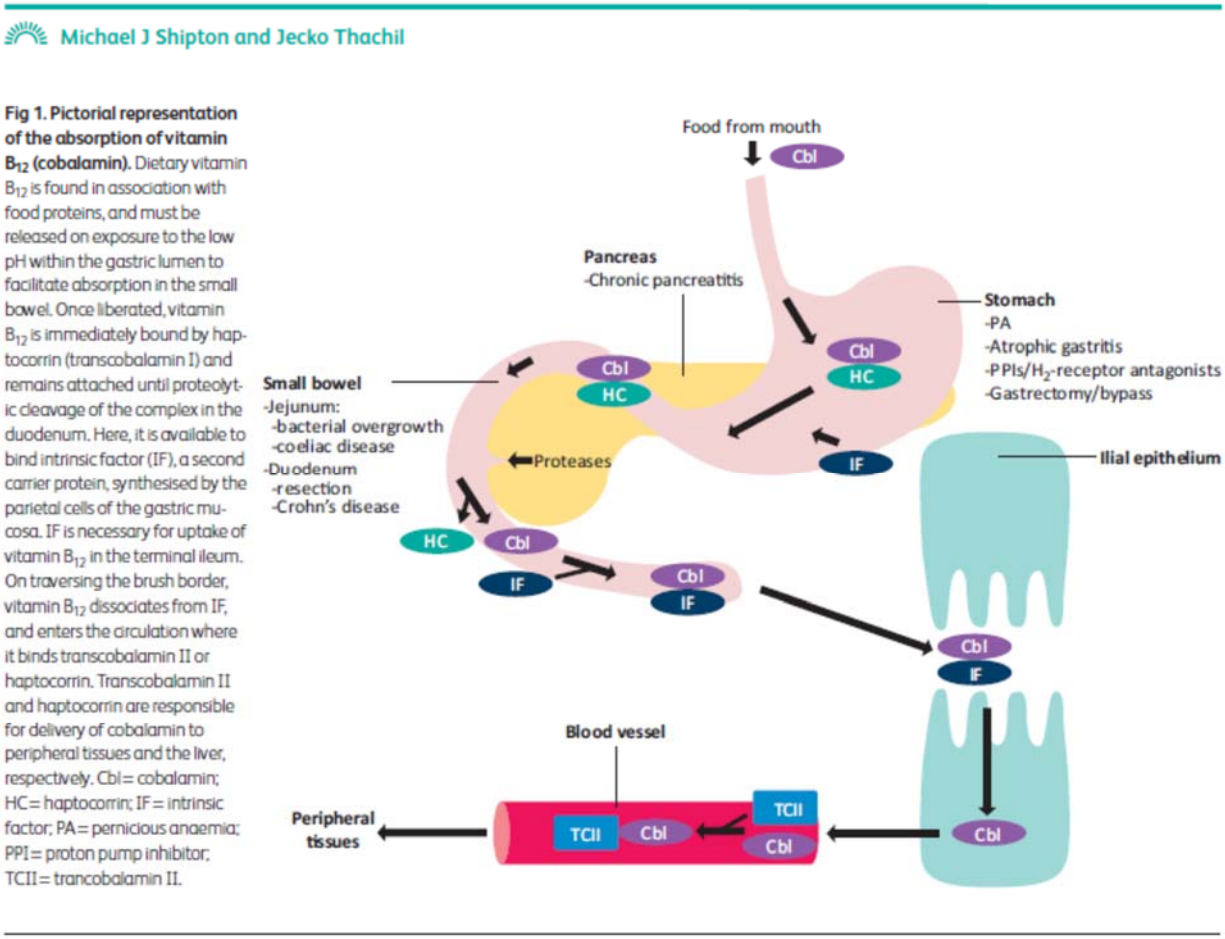


Figure 4 depicts the transport of cobalamin substances into cells and their intracellular metabolism (Paul and Brady 2017). Aspects of the diagram that are most pertinent to this review include:

- Each of the 4 vitamers are absorbed and transported to cells in an inactive form. The pharmacokinetics (PK) of these processes may differ among the vitamers.
- In the cell cytosol, each vitamer is converted to cobalamin, lacking the vitamer ligands.
- A methyl group is then added to cobalamin in the cytosol to convert it to an activated form of methylcobalamin. Many marketed products contain methylcobalamin because it is claimed to be the "active" form of vitamin B_{12}. However, methylcobalamin is not "active" or "activated" until this step in its metabolism.
- Activated adenosylcobalamin is formed from cobalamin in the mitochondria.

Figure 4. Cobalamin at the cellular level (Paul and Brady 2017)

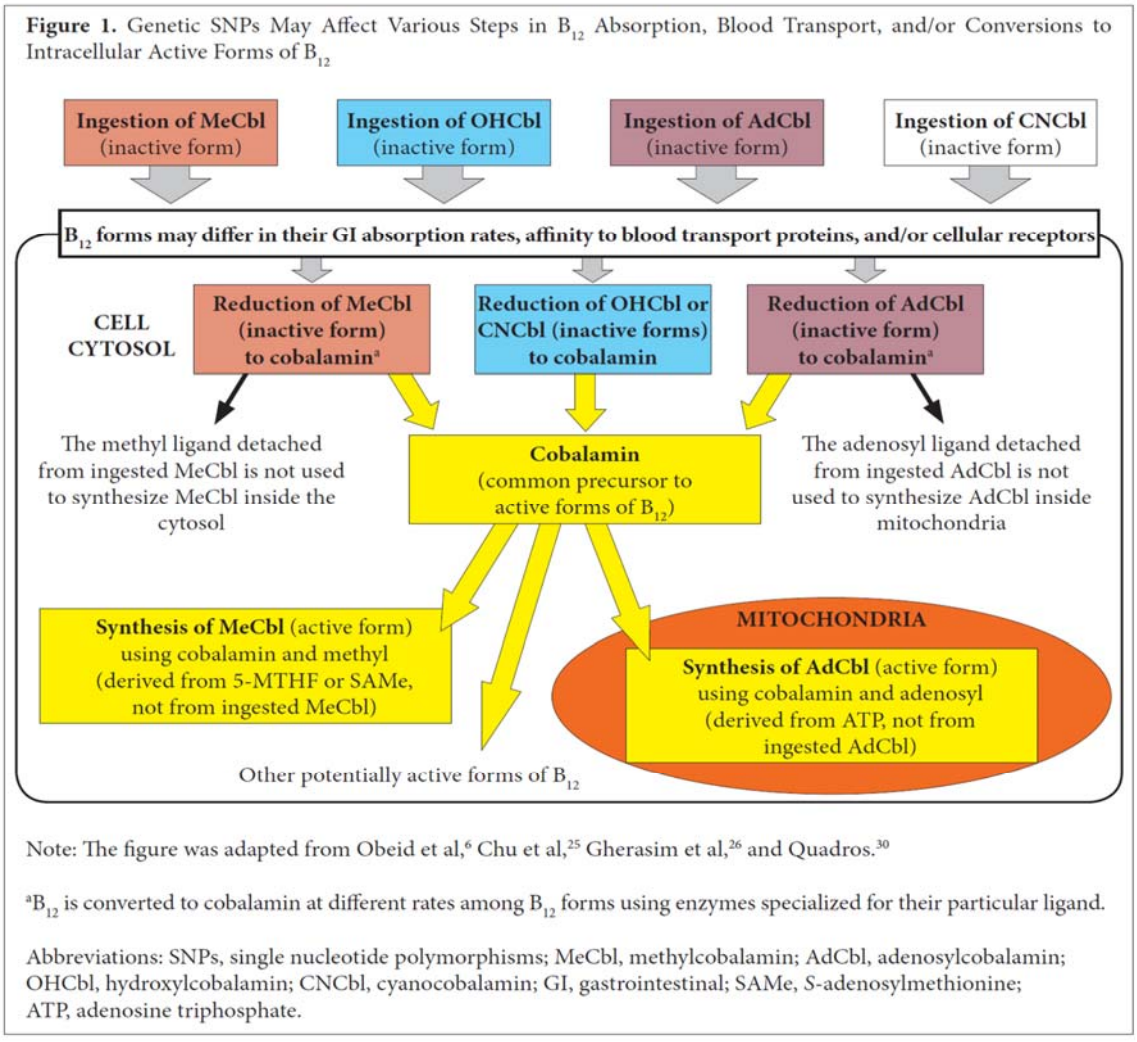


Figure 5 illustrates the primary function of activated methylcobalamin ("B12" in the diagram) as a cofactor for methionine synthase (Spence et al. 2017). This folate-dependent reaction converts homocysteine to methione, which is required for protein synthesis and for the synthesis of S-adenosylmethionine (SAM) a donor for almost 100 different substrates, including DNA, RNA, proteins, and lipids (Allen et al. 2018). The same reaction converts methyltetrahydrofolate to tetrahydrofolate, which is in turn converted to methylenetetrahydrofolate. The latter can serve in the de novo synthesis of thymidylate that is required for DNA replication. A more detailed view of the related processes can be found in Appendix 1, which includes the activity of 5′-deoxyadenosylcobalamin. This cofactor for the mitochondrial enzyme methylmalonyl-CoA mutase, is involved in producing succinyl-CoA for oxidation of fatty acids and catabolism of ketogenic amino acids (Allen et al. 2018).

Figure 5. Methylation of homocysteine to form methionine (Spence et al. 2017)

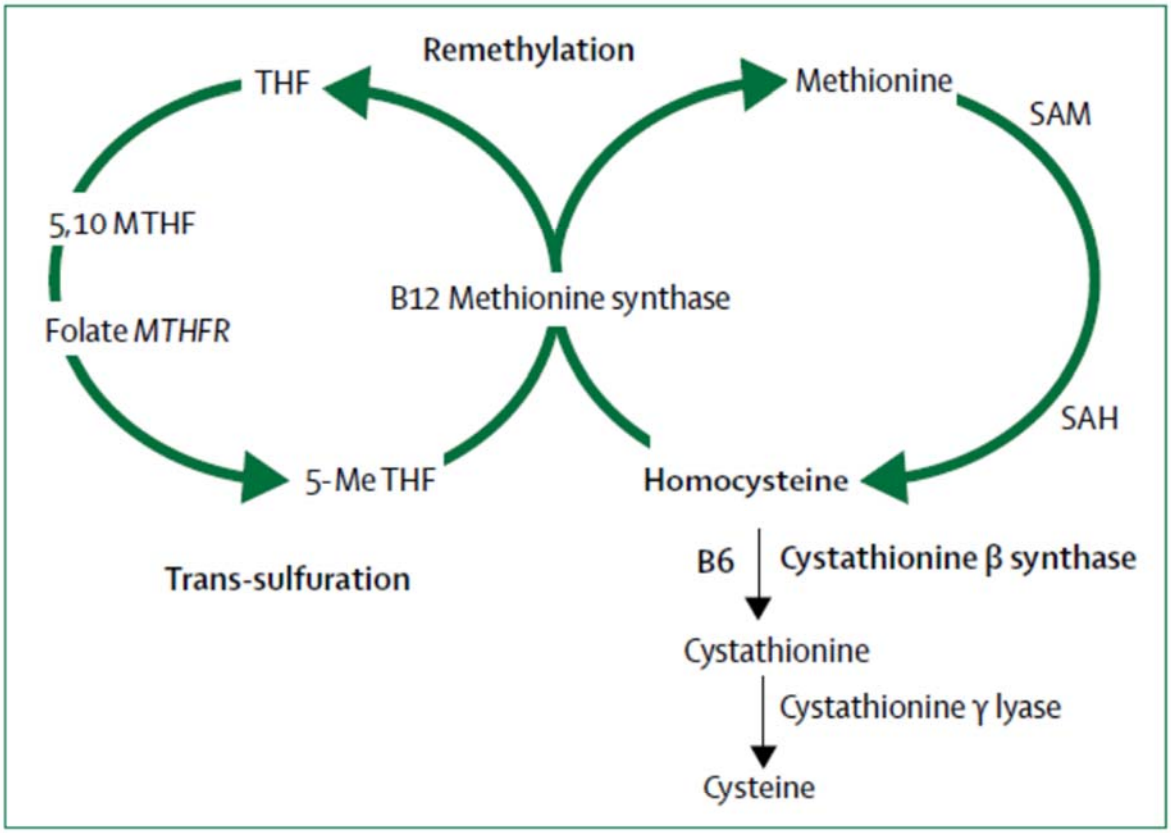


***Figure 1*: Homocysteine metabolism**
B12=cobalamin. B6=pyridoxine. MTH=methylenetetrahydrofolate. MTHFR=methylenetetrahydrofolate reductase. SAM=S-adenosylmethionine. SAH=S-adenosylhomocysteine. 5-Me THF=5-methyl tetrahydrofolate.

Nonclinical studies were found that evaluated pharmacodynamic effects of methylcobalamin in rodents. In streptozotocin-induced diabetic rats, intramuscular administration of methylcobalamin (500 μg/kg body weight/day for 16 weeks but not 50 μg/kg) resulted in decreased demyelination and protection of nerve fiber density and size. Rats were administered intraperitoneal doses of methylcobalamin (50 or 500 μg/kg or 50 μg/kg body weight) and were compared to a vehicle group receiving saline. Only the high-dose (500 μg/kg) methylcobalamin group showed an improvement in the regeneration process of motor neurons (Yagihashi et al. 1984).

The Wobbler mouse model shows similar patterns of neuromuscular deficits and neuropathological findings partially mimicking amyotrophic lateral sclerosis (ALS). When Wobbler mice were administered high doses of methylcobalamin (30 mg/kg/day) by intraperitoneal administration starting from week 3-4 of age daily for 4 weeks, the following results were observed: A significant inhibition of muscle weakness and contracture in the forelimb, and an increase in the weight of the bicep muscles and the number of musculocutaneous nerves. Methylcobalamin-treated mice showed significantly elevated vitamin B_{12} concentrations of the serum, the bicep muscle and the spinal cord compared to vehicle controls (Ikeda et al. 2015).

b. Nonclinical Pharmacokinetics/Toxicokinetics

Following administration of an oral gavage dose (10 ng dissolved in 1 ml) of methylcobalamin or cyanocobalamin, showed similar levels of cobalamin in the small intestines of adult rats. However, significantly more cobalamin accumulated in liver tissue following administration of methylcobalamin when compared to cyanocobalamin (Okuda et al. 1973).

The gastrointestinal distribution and subcellular localization of radioactivity in the ileum of the guinea pig was determined at 2 hrs after oral feeding of physiological doses of cyano-, methyl- and 5' desoxyadenosyl-cobalamin (10-50 ng). The gastrointestinal distribution of the three analogues was similar although the uptake of methyl- and adenosylcobalamin by the ileum was less than that of cyanocobalamin (Peters et al. 1971). See Table 1.

Table 1. Gastrointestinal distribution of labelled cyano-, methyl- and denosylcobalamins (mean percent of oral dose of radioactivity) (Peters et al. 1971)

Organ	*Cyanocobalamin* (IO *ng*)	*Methylcobalamin* (IO *ng*)	*Cyanocobalamin* (50 *ng*)	*Adenosylcobalamin* (*50 ng*)
Stomach and contents	*0.9*	*I.5*	O.IO	0.2
Jejunal contents	o.6	0.3	O.IO	0.2
Jejunal wall	3.5	I.9	0.64	0.3
Ileal contents	I.I	0.4	0.4	0.7
Ileal mucosa	13.5	*6.5*	*5.6*	I.7
Ileal serosa	I.6	0.4	0.3	0.2
Colon and contents	*63.0*	71.9	74.4	81.3
Liver	0.4	0.2	0.2	0.2
Recovery	84.6	82.9	81.6	84.6
No. of experiments	*5*	3	3	3

The PK profile of methylcobalamin in male rats was studied by Tsukerman et al. (1992). Methylcobalamin showed low bioavailability (1% at 1 mg/kg and 1.7 % at 5 mg/kg) after oral dosing. Increasing the dose did not result in a proportional increase in the bioavailability of cobalamins in the body, suggesting saturation. AUC values were found to be similar after oral and intramuscular (IM) dosing, with a range between 500-1000 µg/kg. The elimination half-life (t 1/2) after oral and IM dosing were also similar and averaged ~4-5 hrs. Total serum clearance of cobalamins after dosage with methylcobalamin was only slightly greater (11 ml/min.kg) than the glomerular filtration rate in rats (8 ml/min.kg), suggesting that under the conditions of this study, cobalamin is predominantly excreted in the urine. See Table 2 on the following page.

Table 2. Pharmacokinetic parameters of methylcobalamin in male rats (Tsukerman et al. 1992)

TABLE 2. Pharmacokinetic Parameters of MeCbl

Parameter	P.o. administration using doses of: μg/kg		I. m. administration at a dose of 10 μg/kg
	1000	500	
Time required to reach peak concentration, t_{max}, h	2,0±0,5	0,9±0,2	—
Maximum concentration, C_{max}, nM	1,36±0,64	1,80±0,38	—
Elimination halflife, $t_{\frac{1}{2}}$, h	5,0±2,8	4,0±2,2	3,8±2,4
Mean retention time, MRT, h	8,4±4,0	6,3±3,2	4,2±2,1
Complete absorption time, T, h	2,0±0,5	0,9±0,2	—
Absorption delay time, t_0, h	0,6±0,2	~0	—
Apparent rate constant of elimination, β, h^{-1}	0,14±0,06	0,17±0,08	0,18±0,09
Total clearance, Cl, ml/(min·kg)[a]	11,6±3,0	11,1±2,4	11,1±3,4
Volume of distribution, l/kg[a,b]	V_β=5,0	V_β=3,9	V_β= 3.7 V_1=0,9
Area under the pharmacokinetic curve, AUC, ng/h/ml	10,7±5,4	9,4±3,1	11,1±4,1
Absorbed dose, μg/kg[a]	10	8,5	10
Rate of absorption, μg/(kg·h)	7,1±1,8	9,4±2,1	—
Bioavailability, f, %	1,0	1,7	100
Complex parameter, α, h^{-1} [c]	—	—	0,76
Transfer rate constant, k_{12}, h^{-1} [c]	—	—	1,40
Transfer rate constant, k_{21}, h^{-1} [c]	—	—	0,64

a) Allowing for bioavailability.
b) V_1 is the volume of distribution in the central compartment, V_β is the kinetic volume of distribution.
c) Parameters for the two-compartment model.

A radiolabeled PK study showed that more than 60% of radiolabeled (^{14}C) methylcobalamin disappeared within 2-3 hrs from the gastrointestinal tract of rats when supraphysiological doses of methylcobalamin were used (3.4 μg), suggesting instability of the free methylcobalamin in the gastrointestinal tract when administered exogenously and in large doses. Similar data were obtained when photolyzed ^{14}C methylcobalamin was administered. The authors suggest that the presence of the intrinsic factor, under physiological conditions, may protect the methyl group from cleaving off the cobalamin entity (Okuda et al. 1973).

c. Acute toxicity[3]

The exposure to methylcobalamin at high doses for a short period of time (acute toxicity) was studied in several species and via various routes of administration (anonymous, Kiso to Rinsho 1970). See Table 3. Methylcobalamin was found to be safe when given in high doses.[4]
The lethal dose (LD_{50}) for methylcobalamin in rats and mice using oral, intraperitoneal, and subcutaneous routes of administration delivery is >5 g/kg. The LD_{50} for dogs is >200 mg/kg and

[3] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[4] Table obtained from: https://chem.nlm.nih.gov/chemidplus/rn/13422-55-4#toxicity; original paper "Kisho to Rinsho; Published by Uubunsha" is published in Japanese. No further details were provided on the website.

rabbits is >75 mg/kg, when methylcobalamin is administered via the intravenous route.

Table 3. LD_{50} for methylcobalamin in various animal species (anonymous, Kiso to Rinsho 1970)

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Source
Dog	LD_{50}	intravenous	> 200mg/kg (200mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 22, Pg. 3939, 1988.
Mouse	LD_{50}	intraperitoneal	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Mouse	LD_{50}	oral	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Mouse	LD_{50}	subcutaneous	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Rabbit	LD_{50}	intravenous	> 75mg/kg (75mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Rat	LD_{50}	intraperitoneal	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Rat	LD_{50}	oral	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.
Rat	LD_{50}	subcutaneous	> 5gm/kg (5000mg/kg)	Kiso to Rinsho. Clinical Report. Vol. 4, Pg. 529, 1970.

d. Repeat dose toxicity[5]

No repeat dose toxicity studies were found in the published literature for methylcobalamin.

e Genotoxicity[6]

No mutagenicity studies were found in the published literature for methylcobalamin.

[5] *Repeated-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

[6] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

f. Developmental and reproductive toxicity[7]

No studies were found that tested the effect of exogenous administration of methylcobalamin on fertility, embryofetal or developmental toxicity in animal models.

The deficiency of vitamin B_{12} for 10 weeks suppressed the growth rate of the testis where a decrease in the diameter of the seminiferous tubules in the deficient-diet group was seen. The sperm count and motile sperm count of the vitamin B_{12}-deficient mice were also reduced. When methylcobalamin was administered during a feeding of a vitamin B_{12} deficient diet, the content of vitamin B_{12} in the serum and testis, and all of the above parameters recovered to the control level (Oshio et al. 1992).

g. Carcinogenicity[8]

We did not find any 2-year animal carcinogenicity studies conducted with methylcobalamin in the published literature.

Kal'nev et al. (1978) studied the effect of methylcobalamin (25 and 50 μg/kg) and cyanocobalamin (25 and 50 μg/kg) on the growth of Walker's carcinosarcoma and on the longevity of rats implanted with Zajdela ascites hepatoma (ZAH) cells. The authors reported reduced survival of rats treated with both compounds (~ 20% shorter lifespans compared to controls). The two cobalamins tested shortened the life of rats with implanted tumors of the two types listed above, accelerated the formation of ascites fluid in the case of the implantation of ZAH but did not increase the cell concentration (per unit volume of fluid). The increase in the number of cells occurred through an increase in the volume of the ascites contents.

Conclusions: The available nonclinical data assessing the pharmacology and toxicology aspects of exogenously administered methylcobalamin were limited to pharmacology studies and acute toxicity data assessing lethal doses of methylcobalamin. The open literature does not contain data for repeated dose toxicity, genotoxicity, reproductive/developmental toxicity or 2 year carcinogenicity testing for methylcobalamin.

[7] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

[8] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, ClinicalTrials.gov, FDA Adverse Event Reporting System (FAERS), and the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS).

a. Reported adverse reactions (FAERS, CAERS)

The Office of Surveillance and Epidemiology (OSE) conducted a search of FDA Adverse Event Reporting System (FAERS) for reports of serious adverse events with the term "methylcobalamin," through August 30, 2016. There were 174 reports of serious adverse events (SAEs), including 22 from the U.S. and 152 foreign reports.

Among the United States (U.S.) reports, there were no deaths reported and no events considered by OSE to be probably or certainly related to methylcobalamin. There were four reports that involved methylcobalamin compounded as a single active ingredient product and two were considered by OSE to be assessable based on the amount of information provided by the reporter. In one report, a 38-year-old-male reported that several months after initiating IM dosing with 5,000 µg per week, divided into 4 doses, as part of a physician prescribed protocol for treatment of multiple sclerosis, he developed severe cramps and numbness in one leg. Several months after this, he experienced "tremendous dizziness," "severe amounts of fatigue," shortness of breath and exacerbation of the numbness in his leg. His physician decreased his dose to 2,000 µg per week. The patient reported having intermittently stopped dosing and noticed that his symptoms subsided and he "felt better". He also noted having received a vial of methylcobalamin that was expired per its labeling. He has since requested that his physician order his methylcobalamin from a different compounding pharmacy, one that he had used prior to taking methylcobalamin, and reported that his symptoms have ceased.

In the second assessable U.S. report of a SAE, the mother of a 3-year-old girl reported that her daughter experienced increased liver enzymes and yellowing of hands and feet after receiving compounded methylcobalamin shots for methionine synthetase deficiency for 3 months. No additional information was provided. There were 10 U.S. SAE reports associated with a methylcobalamin product, containing multiple ingredients, marketed as a "dietary food" and eight SAE reports of associated with methylcobalamin as a dietary ingredient in multiple ingredient dietary supplements. The relationship of these cases to methylcobalamin cannot be established based on the reported information.

Of the 152 reports of SAEs from non-U.S. sources, 100 were considered by OSE to be assessable. Of these, none were considered to be probably/likely or certainly associated with methylcobalamin. There was one reported death of a 21-year-old female who was diagnosed with toxic epidermal necrolysis (TEN) after 15 days of treatment with various antibiotics for otitis media followed by 5 days of treatment for rash progressing to Stevens-Johnson syndrome and then TEN. Methylcobalamin was taken orally at 300 mg/day in three divided doses at approximately Days 12 through 15. The patient died 42 days after the TEN diagnosis due to a transfusion-related lung injury. Given the changes in drugs used throughout the first 15 days of her therapy, it is not possible to establish the relationship between methylcobalamin and the

initial presentation of rash. It is noted that "hypersensitivity/rash" is listed in the Adverse Reactions section of the labeling of the approved Japanese methylcobalamin product that the patient received (Methylcobal®) as occurring in < 0.1% of users.

In an updated FAERS review completed December 7, 2020, U.S. only cases regardless of outcome were identified if they were considered "possibly due to methylcobalamin use." Ten cases that met the revised search criteria, but not the previous criteria, were identified.

- Of these 10 cases, 8 non-serious cases were associated with the use of a medical food containing methylcobalamin and other ingredients.[9] Mentax brand was identified in 4 cases for which reports of ageusia that resolved following discontinuation (n = 1), somnolence on first day of use (n = 1), and lack of effect for neuropathy (n = 2). Rheumate brand was reported (n = 1) to have made the reporter's unspecified pain worse and was discontinued. Lexazin brand was ingested and co-administered with topical lidocaine in which reporters (n = 3) experienced hypersensitivity type reactions including application site burn, urticaria, pruritis and erythema.
- In a non-serious case associated with a compounded injectable containing methylcobalamin and other ingredients, the reporter administered a dose from a new vial of medication and experience a headache and "sudden uncontrollable" diarrhea that lasted 2 days. She was subsequently contacted by her compounding pharmacy and told of a recall secondary to "possible contamination."
- In a non-serious case, use of a dietary supplement containing methylcobalamin and folic acid for 3 days with concomitant administration of ondansetron was reported to cause "severe constipation."

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events (AEs) associated with methylcobalamin on August 24, 2020 and 384 reports were identified. Two reports are associated with use of a product that, based on listed ingredients, contained only methylcobalamin with ingredients used to comprise the oral dosage form (e.g., crospovidone to promote dosage form disintegration). In one of these reports, a "customer" stated that he/she had been hospitalized for anxiety and that he/she did not know if the event was related to use of the methylcobalamin product. In the other report involving a presumed methylcobalamin-only product a 75-year-old man took the product for two days, began to feel dizzy and eat poorly. He went to a local emergency department where he was found to be dehydrated and was subsequently treated with several liters of fluid. The patient's condition improved and he discontinued the methylcobalamin product.

The remainder of the reports identify a product or products that were formulated with methylcobalamin and multiple vitamin and/or dietary supplement ingredients such that a causal relationship between methylcobalamin and the AEs cannot be fully evaluated. Six deaths were reported and a brief description of each report is listed below. In none of these reports is there sufficient detail to assess causality.

[9] For more information from FDA about medical foods see: https://www.fda.gov/files/food/published/Guidance-for-Industry--Frequently-Asked-Questions-About-Medical-Foods--Second-Edition-%28PDF%29.pdf

- A "customer" (relationship to deceased was not stated) reported the death was due to a "combination of prescription meds and unknown substance" that "reached toxic levels."
- A "customer" reported that her husband had passed away having "gotten sick when he started taking" a "testosterone booster" product. No additional details were provided.
- The mother of a "male consumer" reported that her son, who had a history of epilepsy, died following approximately 5 months of using a multi-ingredient product before workouts. She reported that his seizure activity had increased following initiation of the product. He was hospitalized following a seizure, was intubated and developed pneumonia and septic shock.
- A retailer reported receiving an email report that "a consumer" died of unknown causes, presumed by the retailer to be a cardiovascular event, after restarting use of a multi-ingredient product after re-starting daily product use following an 11 day break.
- A 33-year-old female "consumer" was reported by a friend to have died following pre-workout use of a multi-ingredient product and an athletic workout. No additional details are provided.
- A patient reported that he and his father have "Factor V Leiden mutation" and both took a multi-ingredient product. His father visited a physician and found that his "blood thinners were not at a therapeutic level" following initiation of the product. It is unclear whether the father discontinued the product based on his physician's advice, but he "died shortly later." Cause of death was not stated.

Reports other than those summarized above describe a wide variety of serious and non-serious AEs, but a causal relationship between methylcobalamin and the AEs cannot be evaluated based on the available information.

b. Clinical trials assessing safety

No published clinical trials were found that were conducted to specifically assess the safety of methylcobalamin in humans. In some studies investigating the use of oral, intramuscular, intrathecal and intravenous methylcobalamin at different doses as a treatment for various disorders, safety data is reported. Adverse events reported with methylcobalamin use are infrequent and non-serious. Adverse events in studies that reported safety outcomes are summarized below.

Two open-label studies in children with ASD reported adverse reactions (James et al. 2009, Frye et al. 2013). The most common AEs observed in each trial were hyperactivity (James 20%, including 2 dropouts; Frye 14%) and reduced sleep (James 2 dropouts for reduced sleep, total rate of sleep-related adverse events 10%; Frye 7%). These were small studies of 40 and 37 children, respectively.

In two placebo-controlled ASD studies, patients in the methylcobalamin treatment arm received either 64.5 µg/kg subcutaneously every 3 days (Bertoglio et al. 2010) for 12 weeks or 75 µg/kg subcutaneously every 3 days (Hendren et al. 2016) for 8 weeks. The Bertoglio trial included a total of 30 children with autism ages 3 to 8. Because this was a cross-over trial, all 30 patients received methyl B_{12} at some point in the trial. The authors list hyperactivity and "mouthing of objects," a behavior of excessive chewing or placing objects in one's mouth that is commonly

seen in ASD patients, as observed AEs. No frequency data are provided and there is no comparison of the incidence between patients on drug versus placebo.

In the Hendren trial 57 children with ASD, ages 3 to 8, were randomized and 50 completed the trial; 27 of the children randomized to methylcobalamin treatment completed the trial. The total number of AEs observed in each treatment group was similar (21 in the methyl B_{12} group versus 24 in the placebo group). The most common AE in the methyl B_{12} group was "mouthing." This was observed in 5 of 27 patients in the methyl B_{12} group compared to 1 of 23 patients in the placebo group. Other AEs that were more frequent in children while on methylcobalamin than placebo were cold, fever, flu, growing pains, increased irritability, and stomach flu; each of these occurred in one additional patient in the methyl B_{12} than in the placebo group. Two patients in the methyl B_{12} group experienced nosebleeds compared to none in the placebo group.

Among studies associated with the other proposed uses considered in this review, safety information was scant:

- Verma et al. (2017) stated that no children receiving oral methylcobalamin supplementation reported AEs.
- Schloss et al (2017) reported that some patients receiving vitamin B_{12} while on cancer chemotherapy found the odor of their urine to be intolerable and vitamin supplementation to increase nausea and vomiting.
- Xu et al (2013) reported one patient on one occasion received a subcutaneous injection of 0.5 mg methylcobalamin in 2 mL and experienced "redness in the face."
- Various studies reported minor pain and hematoma at the site of subcutaneous or intramuscular injections.

c. Other Safety Information

In addition to the study information above, we have considered:

- Safety information from FDA approved labeling for hydroxocobalamin [10] and cyanocobalamin[11] because methylcobalamin might present similar safety considerations due to the apparent commonalities in pharmacologic activity among the cobalamin:

  - Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Folic acid is not a substitute for vitamin B_{12} although it may improve vitamin B_{12}-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B_{12}-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

  - Hypersensitivity. Anaphylactic shock and death have been reported after parenteral vitamin B_{12} administration.

[10] Hydroxocobalamin injection labeling can be found at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3087a39-f218-4f16-a1e7-17c39bb2eb69; Accessed 4/12/2021

[11] Cyanocobalamin injection labeling can be found at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2fb653d6-e2b2-4969-831b-c0dc37b9c0cc; Accessed 4/12/2021

- Acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals.

- Increased blood pressure

- Blunted or impeded therapeutic response to vitamin B_{12} may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties, and concurrent iron or folic acid deficiency.

- Most common adverse reactions (>5%) include transient chromaturia, erythema, oxalate crystals in urine, rash, increased blood pressure, nausea, headache, and infusion site reactions.

- Other adverse events: Asthenia, back pain, generalized pain, chest pain, abdominal or stomach pain, diarrhea, infection, mucosal bleeding, peripheral vascular disorder dyspepsia, glossitis, dysphasia, nausea, vomiting, arthritis, myalgia, abnormal gait, anxiety, fatigue, dizziness, hypoesthesia, incoordination, nervousness, paresthesia, cough, dyspnea, rhinitis, itching, transitory exanthema, feeling of swelling of entire body, and anaphylaxis, and pain after injection.

- The FDA information search identified other information related to adverse reactions and potential drug interactions with methylcobalamin. Drugs.com states that the most common adverse side effects of methylcobalamin are "allergies, nausea, vomiting, diarrhea, loss of appetite, and headache." It also lists the following medications "known to interact with methylcobalamin:" "alcohol, arsenic trioxide, chloramphenicol, cimetidine, dexlansoprazole, esomeprazole, famotidine, lansoprazole, nizatidine, omeprazole, pantoprazole, rabeprazole, ranitidine, and ranitidine bismuth citrate." A website for a compounding pharmacy lists "aminosalicylic acid, colchicine, methformin, neomycin, and grape juice" that "may interact with methylcobalamin." We have no information about how the data on these websites were derived, but we note that potential safety concerns have been identified specific to methylcobalamin.
- Because AE reporting for drug products compounded pursuant to section 503A is generally voluntary for the public and compounding pharmacies, FDA cannot be assured that the use of methylcobalamin injections and infusions in patients (see Section II.D) has not been associated with SAEs.

d. Clinical Pharmacokinetics (PK)

There are limited data regarding the PK of methylcobalamin in any formulation.

The European Food Safety Authority (EFSA) 2000 panel's risk evaluation of methylcobalamin states that cobalamins are generally bioavailable, provided the substance that binds (ligand such as a methyl group for methylcobalamin) to the cobalamin molecule will not cause an induction or inhibition activity of the cobalamin molecule. The EFSA also concluded that the metabolic fate and biological distribution of methylcobalamin is expected to be similar to that of other sources of cobalamin in the diet. The quantity of methylcobalamin or 5'-

deoxyadenosylcobalamin proposed to be used as a food supplement is up to 500 µg vitamin B_{12}/day for adults.

Methylcobalamin has a similar absorption profile to cyanocobalamin following oral administration (Adams et al. 1971), suggesting that the substances may be interchangeable with respect to systemic delivery of cobalamin. Bioavailability of vitamin B_{12} is generally inversely proportional to the consumed dose, due to the saturation of the receptors that mediate endocytosis of the intrinsic factor-cobalamin complex into the ileal enterocyte (Allen 2010).

It is estimated that most cobalamin enters the body via nutrition. Several milligrams are stored in the liver and this amount is generally sufficient to address the daily need for cobalamin, without supplementation, under normal fed conditions. Only 0.1 - 0.2% of cobalamin is lost per day due to metabolic activity. Cobalamin will further accumulate in liver tissue following exogenous administration of methylcobalamin (European Commission Scientific Committee on Food (SCF) 2000).

In a non-U.S. clinical PK study, the administration of supplemental methylcobalamin increased its serum levels (Akkus Arslan et al. 2013). An oral nanoemulsion under investigation was found to be slightly more bioavailable than a commercial tablet form and close to the bioavailability of a commercial parenteral form and it can be concluded that the type of oral dosage form may affect bioavailability. See Table 4.

Table 4. Pharmacokinetic profile of methylcobalamin in serum samples (Akkus Arslan et al. 2013)

Dose (µg/kg)	**t_{max} (hour)**	**Administration way**	**Formulation type**	**Form of B_{12}**	**Mean serum concentration* at t_{max} (pg/mL) (n=3, ˜X±SS)**
15	2	Oral	Nanoemulsion	Methylcobalamin	4250 ± 2
		Intramuscular	Parenteral	Cyanocobalamin	4570 ± 5
		Oral	Tablet	Cyanocobalamin	3950 ± 3

* The serums were analyzed by using 'rat, vitamin B_{12}, ELISA, Cusabio kits' using 1/100 dilution.

Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating greater tissue retention of methylcobalamin compared to vitamin B_{12} (Okuda et al. 1973; cited in Alternative Medicine Review, 1998). The main excretion of vitamin B_{12} is through the bile, but there is a considerable reabsorption in the ileum of biliary cobalamin due to enterohepatic circulation. Average daily losses via the stool are estimated at ~0.5 µg/day (SCF 2000).

Vitamin B_{12} has been found to be transferred across the placenta such that low maternal B_{12} levels (e.g., as low as 120 – 180 pmol/L) can be associated with fetal B_{12} deficiency as well as issues in both fetal and child development, per a review by Pepper and Black (2011). In one study included in the review, a group of mothers had a significantly lower median B_{12} level of 67 pmol/L at 28 weeks gestation (Group 1) when compared to another group of mothers who had a normal median B_{12} level of 278 pmol/L at 28 weeks gestation (Group 2), $p<0.001$ (Bhate et al. 2008). The in utero exposure to B_{12} correlated with the median B_{12} levels of the two groups of children at 6 years of age where the children's B_{12} levels were 216 and 246 pmol/L, respectively, $r = 0.16$, $p<0.001$, showing a statistically significant difference in median B_{12} levels ($p<0.001$) between Group 1 and Group 2. Neurocognitive development measures for children in Group 1 at age 9 were found to be statistically and significantly lower than for Group 2 with respect to short term memory function and sustained visual attention. These results were found after controlling for the child's age, gender, socioeconomic status, head circumference, weight, and B_{12} status at age 6. The authors suggest that these findings support standard vitamin B_{12} supplementation during pregnancy, as with current standard folic acid supplementation.

e. Availability of alternative approved therapies that may be as safe or safer

The FDA-approved cyanocobalamin and hydroxocobalamin products are considered to be safe treatment of patients with vitamin B_{12} deficiency and certain inborn errors of metabolism, as specified in the FDA approved labeled indications.[12]

[12] Consistent with its practice as stated in the Notice of Proposed Rulemaking entitled "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," published in the Federal Register of December 16, 2016 (81 FR 91071, 91075), FDA in its discretion opted to evaluate the unproposed use of treatment of vitamin B_{12} deficiency, generally aligned with the FDA approved labeled indications for cobalamin drugs and not otherwise associated with nominator-proposed uses.

Hydroxocobalamin injection

I. Pernicious anemia, both uncomplicated and accompanied by nervous system involvement.
II. Dietary deficiency of Vitamin B_{12}, occurring in strict vegetarians and in their breast-fed infants.(Isolated vitamin B deficiency is very rare).
III. Malabsorption of vitamin B_{12}, resulting from structural or functional damage to the stomach, where intrinsic factor is secreted or to the ileum, where intrinsic factor facilitates vitamin B_{12} absorption. These conditions include tropical sprue, and nontropical sprue (idiopathic steatorrhea, gluten-induced enteropathy). Folate deficiency in these patients is usually more severe than vitamin B_{12} deficiency.
IV. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B_{12} deficiency. Structural lesions leading to vitamin B_{12} deficiency include regional ileitis, ileal resections, malignancies, etc.
V. Competition for Vitamin B_{12} by intestinal parasites or bacteria. The fish tapeworm (Diphyllobothrium latum) absorbs huge quantities of vitamin B_{12} and infested patients often have associated gastric atrophy. The blind-loop syndrome may produce deficiency of Vitamin B_{12} or folate.
VI. Inadequate utilization of vitamin B_{12}. This may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.
VII. For the Schilling Test.

Hydroxocobalamin is also available in a kit for injection indicated for the treatment of known or suspected cyanide poisoning.

Cyanocobalamin injection

Cyanocobalamin is indicated for vitamin B_{12} deficiencies due to malabsorption which may be associated with the following conditions:

- Addisonian (pernicious) anemia
- Gastrointestinal pathology, dysfunction, or surgery, including gluten enteropathy or sprue, small bowel bacteria overgrowth, total or partial gastrectomy
- Fish tapeworm infestation
- Malignancy of pancreas or bowel
- Folic acid deficiency

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see **Drug Interactions**), use of a gluten-free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of cyanocobalamin.

Requirements of vitamin B_{12} in excess of normal (due to pregnancy, thyrotoxicosis, haemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with oral supplementation.

Cyanocobalamin Injection, USP is also suitable for the vitamin B_{12} absorption test (Schilling test).

Cyanocobalamin for nasal delivery

Nascobal Nasal Spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement.

Nascobal Nasal Spray is also indicated as a supplement for other vitamin B_{12} deficiencies, including:

1. Dietary deficiency of vitamin B12 occurring in strict vegetarians (Isolated vitamin B12 deficiency is very rare).
2. Malabsorption of vitamin B12 resulting from structural or functional damage to the stomach, where intrinsic factor is secreted, or to the ileum, where intrinsic factor facilitates vitamin B12 absorption. These conditions include HIV infection, AIDS, Crohn's disease, tropical sprue, and nontropical sprue (idiopathic steatorrhea, gluten-induced enteropathy). Folate deficiency in these patients is usually more severe than vitamin B12 deficiency.
3. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis, HIV infection, AIDS, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B12 deficiency. Structural lesions leading to vitamin B12 deficiency include regional ileitis, ileal resections, malignancies, etc.
4. Competition for vitamin B12 by intestinal parasites or bacteria. The fish tapeworm (Diphyllobothrium latum) absorbs huge quantities of vitamin B12 and infested patients often have associated gastric atrophy. The blind loop syndrome may produce deficiency of vitamin B12 or folate.
5. Inadequate utilization of vitamin B12. This may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see Drug/Laboratory Test Interactions), use of a gluten free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B12.
Requirements of vitamin B_{12} in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with intranasal or oral supplementation.
Nascobal Nasal Spray is not suitable for vitamin B_{12} absorption test (Schilling Test).

There are also number of approved injectable multivitamin products that contain cyanocobalamin that are FDA approved and safe to be used to treat vitamin B_{12} deficiency.

There are no drugs approved to treat the core symptoms of ASD. Two drugs—risperidone and aripiprazole—are approved for the treatment of irritability associated with autism. Labeled warnings associated with both of these drugs include metabolic changes, neuroleptic malignant syndrome, and tardive dyskinesia, among others. Common adverse reactions include akathisia, extrapyramidal symptoms, and weight gain.

There are two drugs that have been approved by FDA to slow the progression of ALS, riluzole and edaravone.

Numerous topical, oral and injectable medications are FDA approved to treat pain associated with peripheral neuropathies and other conditions. They have a wide variety of adverse effects, some of which are serious, depending on dose and duration of treatment.

Folic acid, vitamin B_9, is used for treatment for hyperhomocysteinemia and vitamin B_{12} may be added to treatment. Hyperhomocysteinemia is not an FDA approved indication for hydroxocobalamin or cyanocobalamin.

Conclusions: The available nonclinical data assessing the pharmacology and toxicology aspects of exogenously administered methylcobalamin were limited to basic pharmacology studies. Acute toxicity data that showed methylcobalamin to be safe when administered at high doses for short periods of exposure.

No published clinical studies have been found that were specifically conducted to assess the safety of compounded methylcobalamin in humans. In addition, no studies were found that compared the safety of the various cobalamin substances. Studies of methylcobalamin efficacy and safety either did not report adverse effects or reported few adverse effects associated with therapy. Most studies were conducted with only few individuals (<20 per study) and relatively short exposure ($\leq$ 12 weeks). Some studies were not designed with a control treatment. There were various routes of administration and doses used among the studies. The absence of reported adverse reactions was due to a variety of reasons: adverse reactions were not collected, not reported, or not observed. In many reports, there was a general statement about safety of the treatments, but no data to support the statement.

FAERS and CAERS data did not identify serious adverse effects that could be causally linked to methylcobalamin.

Overall, we have sufficient data to characterize the safety of FDA approved cobalamin substances. Methylcobalamin is found in foods and oral use of methylcobalamin as a dietary supplement does not appear to be associated with SAEs.

Based on the likely comparability of the mechanism of action of methylcobalamin to cyanocobalamin and hydroxocobalamin, and the listing of serious adverse events in the FDA approved labeling for cyanocobalamin and hydroxocobalamin, serious adverse effects could

occur with methylcobalamin use. We have a concern regarding the lack of available safety data, particularly of intravenous injections and infusions, used for a variety of conditions, some of which are serious, (see Section II.D). Specific information supporting the safety of injectable methylcobalamin could not be found.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed and ClinicalTrials.gov.

Nominations and our literature review identified a number of disorders in which the effectiveness of treatment with methylcobalamin has been evaluated (Gupta and Sana 2015). This review considers treatment of vitamin B_{12} deficiency caused by insufficient dietary intake or age associated reduction of absorption; autism spectrum disorder; amytrophic lateral sclerosis; diabetic, uremic and chemotherapy-induced peripheral neuropathy; various pain conditions; hyperhomocysteinemia, and inborn errors of metabolism including MTHFR polymorphisms and conditions affecting cobalamin absorption and metabolism. Information for the efficacy portion of this review was derived from searches of the PubMed database. Many review articles cited in this document encompass other database sources.

It has been observed that for conditions which require supplementation with injectable cobalamin, the U.S. employs cyanocobalamin or hydroxocobalamin as the vitamers of choice, while in Asia methylcobalamin is the most widely used cobalamin (Obeid et al. 2019). Although there is little clinical information comparing the safety and efficacy of the cobalamins, these use patterns may be primarily related to availability (Kamath and Pemminati 2017) and cost. These considerations may be helpful in considering the treatments selected for the clinical studies discussed in this review.

Information for each use is provided in the following format:

(1) Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance
(2) Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease.
(3) Whether there are any alternative approved therapies that may be as effective or more effective.

FDA conclusions based on the related information is at the end of each reviewed use section.

1. Vitamin B_{12} Deficiency

(1) Vitamin B_{12} deficiency in the U.S. and the United Kingdom, is defined as a serum level of B_{12} less than approximately 111 - 148 pmol/L, depending on the standards among different institutions. Vitamin B_{12} deficiency is most common among older individuals and has a prevalence of approximately 5% in persons age 60 years or older (Allen 2018). It can be associated with a variety of causes, such as limited dietary intake of vitamin B_{12} due vegetarian or vegan diets that lack animal products, disorders causing malabsorption such as Crohn's

disease or long term use of drugs such as metformin or histamine H2 blockers. Decreased cobalamin absorption can be due to age or chronic autoimmune gastritis targeting parietal cells or intrinsic factor (Langan and Goodbred 2017). Substantial deficiencies can cause pernicious anemia. Inborn errors of metabolism that are associated with vitamin B_{12} deficiency are discussed in the subsequent section of this review.

Common clinical signs and symptoms of vitamin B_{12} deficiency include changes in skin pigmentation, peripheral neuropathy, anemias due to effects on bone marrow, and cognitive impairment such as dementia-like symptoms. Testing of various hematologic and clinical chemistry parameters can be necessary to diagnose vitamin B_{12} deficiency, distinguishing it other vitamin deficiencies and causes of anemia. Vitamin B_{12} deficiency is treated with B_{12} supplementation. In the U.S., dosing is typically 1000 µg cyanocobalamin several times a week via intramuscular (hydroxocobalamin, cyanocobalamin) or subcutaneous (cyanocobalamin only) injection for 1 – 2 weeks, then weekly until there is clear improvement, followed by monthly injections thereafter (Stabler 2013).[13] Intravenous use is not advised, per FDA approved labeling. These injections can be self-administered by the patient. High dose daily oral therapy (500 – 2000 µg) with cyanocobalamin dietary supplement products has also been shown to be effective therapy (Vidal-Alaball et al. 2005). Treatment duration is primarily dependent on the cause of the deficiency and can be lifelong.

Use of methylcobalamin for the treatment of vitamin B_{12} deficiency has been described in India, where the oral methylcobalamin is "more easily available" than oral cyanocobalamin (Kamath and Pemminati 2017); the authors recommended that a well-designed controlled clinical trial is needed to compare various forms of B_{12}.

- In an observational study conducted in New Delhi of 28 children, B_{12} deficiency was defined by hematologic assessment (macrocytic anemia) and confirmed by low holotranscobalamin levels14 (Verma et al. 2017). One month treatment with oral methylcobalamin at doses of 30 µg/kg/day in children ranging from 6 months to 18 years (half were under the age of 1 year) was associated with significant improvement in mean hemoglobin, mean corpuscular volume, absolute reticulocyte count and platelets compared to baseline. Low holotranscobalamin was corrected after one month in 27 of the children. Vitamin B_{12} levels were low in 19 of the 27 children and correction was observed following one month of treatment in each.
- Thakkar and Billa (2015) do not provide clinical data, but recommend that treatment with vitamin B_{12} consist of cyanocobalamin, hydroxocobalamin, or a combination of methylcobalamin and adenosylcobalamin, as these treatments are considered by the authors to be necessary to address the various functions of vitamin B_{12} metabolites in the body. A subsequent publication finds that the need for treatment with both methylcobalamin and adenosylcobalamin is not supported (Verma et al. 2017).

[13] Dosing recommendations in FDA approved labeling are generally lower but specify that "higher doses may be indicated".

[14] Holotranscobalamin (holoTC) is cobalamin in the serum that is bound to transcobalamin. It is approximately 20% of the body's total serum cobalamin. The other 80% is bound to circulating haptocorrin. Holotranscobalamin levels are an early marker of vitamin B_{12} deficiency that is more sensitive and specific than total serum cobalamin (Hermann and Obeid 2012).

- An English abstract is available for a report of the treatment of 17 patients with methylcobalamin in Japan with "vitamin B12 deficiency anemia." Initial treatment doses were not reported, but maintenance oral doses of 1,500 μg daily were used for 1 to 3 months. It is stated that "correction of hematological and neurological abnormalities was prompt" and long term treatment with methylcobalamin was effective (Takasaki et al. 2002).
- Two trials conducted outside of the U.S. were identified in ClinicalTrials.gov to have evaluated methylcobalamin supplementation to treat vitamin B12 deficiency (NCT01661309, NCT00165711). These trials were reported to have been completed, but no related published information has been identified.
- As previously stated, it has been observed that for conditions which require supplementation with injectable cobalamin, the U.S. employs cyanocobalamin or hydroxocobalamin as the vitamers of choice, while in Asia methylcobalamin is the most widely used vitamer (Obeid et al. 2019).

(2) Vitamin B12 deficiency and pernicious anemia can be severe and life threatening, particularly in situations where diet is poor and medical treatment is not readily available. Most cases in the U.S. are easily identified and successfully treated.

(3) Hydroxocobalamin is FDA approved as an injectable drug in the U.S., indicated to treat vitamin B12 deficiency (intramuscular administration). Cyanocobalamin injectable (intramuscular or subcutaneous administration) and nasal products are also FDA approved and can be used to treat vitamin B12 deficiency. In some cases, supplementation with oral vitamin B12 may be sufficient.

Conclusions: The pharmacologic mechanism of methylcobalamin suggests that it is likely to be effective in treating vitamin B12 deficiency. No U.S. clinical studies of methylcobalamin use to treat vitamin B12 deficiency were found, likely due primarily to the availability of two FDA approved alternative cobalamins in the U.S. However, clinical studies from outside of the U.S., where methylcobalamin is the more commonly used cobalamin substance, provide some evidence that methylcobalamin is effective for treatment of vitamin B12 deficiency. Neither U.S. nor non-U.S. studies have been identified that compare the effectiveness of methylcobalamin to treat vitamin B12 deficiency relative to other cobalamins. We found no data that show hydroxocobalamin or cyanocobalamin are insufficient to provide treatment for vitamin B12 deficiency.

2. Inborn errors of metabolism

(1) Many nutritional, acquired and inborn disorders can affect the absorption, transport in the blood, intracellular metabolism or physiologic action of cobalamin (Hermann and Obeid 2012). A table summarizing the genetic and biochemical markers of these disorders is in Appendix 2 (Huemer and Baumgartner 2019). Table 5 provides more detailed information about the onset, treatment and outcomes of each disorder.

Table 5. Deficiencies and disorders that affect cobalamin (Huemer and Baumgartner 2019)

TABLE 2 Age at presentation, treatment and outcome in Cbl-associated diseases, MTHFR deficiency and the MTHFD1 defect (for references see text)

Disorder / defect	Typical age at onset	Treatment approaches	Outcome
Neonatal Cbl deficiency	First months of life	Start with parenteral Cbl generally preferred	**All:** Only favourable if treated in a timely fashion
Nutritional Cbl deficiency	Any age	Start with parenteral Cbl generally preferred	Residual damage in severe presentation / late diagnosis
Cbl deficiency due to IF / gastric parietal cell antibodies	Adulthood	Parenteral Cbl	
Inborn errors of cobalamin absorption and systemic trafficking			
Gastric intrinsic factor deficiency	Preschool years	Parenteral Cbl, single cases with oral treatment	Generally favourable
Imerslund-Gräsbeck syndrome (IGS)	Variable, from infancy to adolescence	Parenteral Cbl	Generally favourable; proteinuria persists
Transcobalamin deficiency	Early infancy	Parenteral Cbl	Favourable with early treatment
Haptocorrin deficiency	Asymptomatic	?	Favourable without treatment
Transcobalamin receptor	Probably asymptomatic	?	Excellent Some individuals treated with Cbl
Inborn errors of intracellular cobalamin metabolism and trafficking			
cblA	**All disorders:** Majority <12 months; many neonatal presentations but late-onset cases described	Parenteral OH-Cbl, in some patients switch to oral treatment possible	Mostly favourable
cblB		Parenteral OH-Cbl if responsive	Intermediate
cblD-MMA		Parenteral OH-Cbl if responsive	Very few cases
cblF cblJ cblC cblD-MMA-HCY cblD-HCY cblE cblG		**cblF, cblJ, cblC, cbl-MMAHCY, cblD-HCY, cblE, cblG:** Parenteral OH-Cbl , betaine (carnitine in combined disorders and folate/ folinate often added)	**cblF, cblJ, cblC, cbl-MMAHCY, cblD-HCY, cblE, cblG:** - Patients presenting with aHUS /PAH have high mortality - Under treatment • Microangiopathy, metabolic crises and mortality reduced • Eye disease and cognitive impairment unchanged or progressive
Inborn errors of folate metabolism interfering with remethylation			
MTHFR deficiency	Majority < 12 months Many neonatal presentations Late-onset cases described	Betaine (Folinate; rarely 5-MTHF added)	Early betaine preventive
MTHFD1 deficiency	Neonatal or in early infancy	Folinate and folic acid	Good immunological response to treatment Very few cases

Abbreviations: Cbl, cobalamin; IF, intrinsic factor; IGS, Imerslund-Gräsbeck syndrome; MMA, methylmalonic acid; MTHFD1, methylenetetrahydrofolate dehydrogenase; MTHFR, methylene tetrahydrofolate reductase.

- Cobalamin absorption

Cobalamin deficiency due to insufficient dietary intake and age-related decreases in intrinsic factor have been previously discussed in this review. There are other inherited defects that compromise cobalamin (i.e., any of the 4 vitamers) absorption, including congenital pernicious anemia due to an inability to synthesize intrinsic factor and Imerslund-Gräsbeck syndrome decreasing cobalamin transfer from intestinal cells to the bloodstream. Both are treated with a

lifelong injectable form of vitamin B12 (Gräsbeck 2006). No information was found regarding treatment with methylcobalamin.

- Cobalamin transport in the bloodstream

Congenital transcobalamin deficiency results in a decreased capacity to transport cobalamin to cells where it is used. Haptocorrin contributes to cobalamin transport in the plasma and patients are treated with injectable cobalamin to maximize use of the existing low levels of transcobalamin (Huemer and Baumgartner 2019). No information regarding treatment with methylcobalamin was identified.

- Cobalamin intracellular metabolism

Various diseases result from rare inborn errors in the ability to process cobalamin in the intracellular environment, both in the cytosol and mitochondria (Herrmann and Obeid 2012). These disorders were named in the order they were identified and coded "Cbl-" a, b, etc. See Figure 6 for an illustration of the metabolic steps that are compromised in some of these disorders. Table 5 lists these inborn errors and their treatment. Treatment in the U.S. with "Cbl" (either hydroxocobalamin or cyanocobalamin) or "OH-Cbl" (hydroxocobalamin), is intended to prevent buildup of substances that cannot be metabolized in the cell (e.g., methylmalonic aciduria/acidemia, also called CblD-MMA or MMA)) or provide additional cobalamin substrate to enhance functionality. One study compared treatment of MMA with intramuscular cyanocobalamin to intravenous hydroxocobalamin, finding the latter more effective (Andersson and Shapira 1998). No information regarding treatment with methylcobalamin was identified.

Figure 6. Cobalamin metabolic disorders (Herrmann and Obeid 2012)

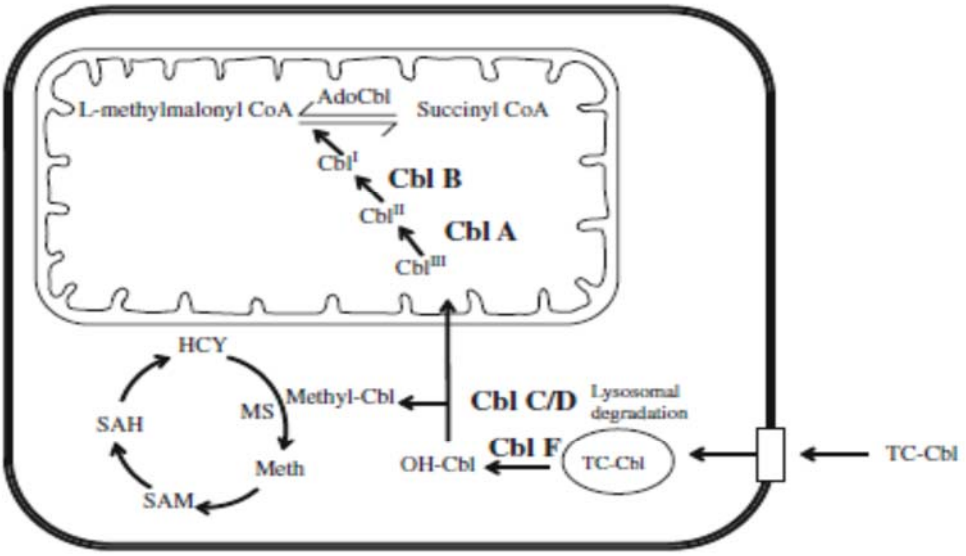


Fig. 16.1 The metabolic pathways enhanced by cobalamin and inherited disorders of cobalamin (see text for details). Hcy; homocysteine, Met; methionine, SAH; S-adenosylhomocysteine, SAM; S-adenosylmethionin, methyl-Cbl; methyl cobalamin, Ado-Cbl; adenosyl cobalamin

- Methylene-tetrahydrofolate reductase (MTHFR) deficiency

MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahdryofolate, the active form of folate and a co-substrate for homocysteine remethylation to methionine (see Figure 5). MTHFR deficiency and MTHF dehydrogenase (MTHFD1) deficiency are diseases caused by inborn errors of metabolism that result in homocysteinuria and can be fatal (Huemer et al. 2017). They are treated with FDA approved betaine and folic acid. No information regarding treatment with methylcobalamin was identified.

There are also many known polymorphisms of the MTHFR gene that have unclear clinical consequences. They can be associated with low levels of active folate and increased homocysteine plasma levels (Miranda-Massari et al. 2011). Various MTHFR deficiency health outcomes that have been studied, with conflicting results, include cardiovascular disease, recurrent pregnancy loss, neural tube defects, increased cancer risk and neurodevelopmental and neuropsychiatric risk (Levin and Varga 2016). The general approach to addressing MTHFR polymorphisms is to increase folate intake with folic acid fortified grain products, a program initiated in the U.S. in 1998, or with folic acid supplements (Levin and Varga 2016). In one case report, a patient undergoing oral therapy for hypothyroidism presented to a family medicine practitioner with complaints of anxiety. Her symptoms resolved following 6 months of recurrent visits to the practice and titration of oral treatments including thyroid supplementation, methylcobalamin, B vitamin complex, L-5-MTHF, SAM-e and Ativan (Anderson et al. 2016). The authors emphasize the need for careful adjustment of various treatment components in

MTHFR. The contribution of methylcobalamin to the patient's treatment is unclear given the multiple concomitant therapies and titration steps.

- Classic Homocystinuria

Homocysteine is an intermediate in the folate cycle. See Figure 5 or Appendix 1. It is not an essential amino acid, cannot be acquired through food intake, and is biosynthesized from methionine (Selhub 1999). Homocysteine that does not undergo conversion to methionine is normally degraded to cysteine via cystathione beta synthase (Blom and Smulders 2011). An inborn error of metabolism that causes a deficiency of this enzyme (cystathione beta synthase deficiency, also called classic homocystinuria) results in decreased conversion of homocysteine to cysteine, an increase in homocysteine, and homocystinuria. Homocystinuria can also occur with MMA. MMA, classic homocystinuria, and MMA with homocystinuria are each treated with hydroxocobalamin. No information regarding treatment with methylcobalamin was identified.

(2) Untreated, cobalamin absorption and transport disorders can be life threatening. Most of these disorders appear responsive to treatment with a cobalamin product, although these indications are not in FDA approved labeling. Intracellular metabolism disorders have variable degrees of severity, often correlated with the age of onset or diagnosis. Similarly, response to treatment is variable (more severe in younger patients) and can be life threatening. MTHFR and MTHFD1 deficiency can be a life threatening or fatal diseases. MTHFR polymorphisms have not been consistently linked with serious health conditions and are not life threatening. Homocystinuria, MMA and the combination can be life threatening or fatal.

(3) Inborn errors of metabolism, if treated with cobalamin, are generally addressed in the U.S. with administration of hydroxocobalamin. MTHFR deficiency and MTHFD1 deficiency are treated with FDA approved betaine or folate supplementation.

Conclusions: Hydroxocobalamin and cyanocobalamin are used to some treat inborn errors of metabolism of cobalamin absorption, transport or activity. No clinical studies were found that support the effectiveness of methylcobalamin to treat inborn errors of metabolism.

3. Hyperhomocysteinemia

(1) Hyperhomocysteinemia as referred to in this section is not associated with the inborn error of metabolism that was previously described. Disorders that may cause hyperhomocysteinemia include chronic renal failure, hypothyroidism, certain malignant tumors, pernicious anemia and sickle cell anemia (Kim et al. 2018). Drugs can also cause hyperhomocysteinemia: cholestyramine, metformin, methotrexate, nicotinic acid (niacin), fibric acid derivatives (to lower blood triglycerides) and oral contraceptives. Hyperhomocysteinemia is cause for concern as homocysteine can damage endothelium and other tissues. Hyperhomocysteinemia has been associated with contributing to the cause of various disorders including atherosclerosis (Sreckovic et al. 2016), congestive heart failure (Cooke et al. 2000), age-related macular degeneration (Rochtchina et al. 2007), Alzheimer's disease (Seshadri et al. 2002) and cancer (Plazar and Jurdana 2010).

Average homocysteine plasma levels are 10 to 15 μmol/L in the general population. The Homocysteine Lowering Trialists' Collaboration (2005) showed in a meta-analysis of 25 randomized trials that treatment of healthy individuals with folic acid reduced homocysteine levels by 25%. The design of 9 of these trials included treatment with vitamin B_{12}, which reduced homocysteine levels by an additional 7%. However, in patients with cardiovascular disease, neither the occurrence of cardiovascular events nor mortality were reduced by treatment with these cofactors. In one double blind, placebo-controlled study (the Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial), 5522 patients with vascular disease or diabetes were randomized to receive an oral dose of placebo or the combination of 2.5 mg of folic acid, 50 mg of vitamin B_6 and 1 mg of vitamin B_{12} (Lonn et al. 2006). No mention is made regarding dosing with or measurement of methylcobalamin specifically. Participants were followed for an average of five years. Mean plasma homocysteine levels were the same in both groups, 12.2 μmol/L at baseline, and decreased by 2.4 μmol/L in the vitamin treated group and increased 0.8 μmol/L in the placebo group at the end of the study. Primary outcome events (death from cardiovascular causes, myocardial infarction, stroke) occurred in 519 patients (18.8%) of active treatment patients and 547 (19.8%) placebo patients (relative risk 0.95; 95% confidence interval, 0.84 to 1.07; P=0.41). Additional research is needed to fill information gaps such as why familial hyperhomocysteinemia is not causally linked with coronary heart disease (de Craen et al. 2006); whether stroke outcomes may benefit more than other cardiovascular outcomes from treatment with B vitamins and folic acid (Refsum and Smith 2006), and whether duration of pre-existing cardiovascular disease, treatment duration and treatment doses of B vitamins and folic acid may impact the associations (Quinlivan and Gregory 2006; Wang et al 2006).

Hyperhomocysteinemia is diagnosed when homocysteine levels are above 15 μmol/L and is classified as moderate (15 to 30 μmol/L), intermediate (30 to 100 μmol/L) or severe (greater than 100 μmol/L) (Maron and Loscalzo 2009). Approximately 85% of patients with chronic kidney disease (CKD) also have hyperhomocysteinemia, due to impaired renal metabolism, reduced renal excretion and, often, insufficient intake of folic acid (de Koning and Hu 2010; Cianciolo et al. 2017).

Hyperhomocysteinemia has been found to be an independent predictor of cardiovascular morbidity and mortality in end-stage renal disease (ESRD), based on a meta-analysis of 28 studies of patients on hemodialysis or peritoneal dialysis not receiving vitamin B complex or folic acid supplementation (Heinz et al. 2009). Maximal homocysteine lowering in ESRD has been associated with use of 1 to 2 mg daily of oral folic acid (van Guldener 2006). Vitamin B_6 does not substantially impact plasma homocysteine levels in dialysis patients, but vitamin B_{12} "may lower homocysteine somewhat further when added to folic acid, especially in patients with subclinical B_{12} deficiency" (van Guldener 2006). Based in part on these conclusions, Nigwekar et al. (2016) reviewed six studies of 2452 participants with ESRD to determine the "benefits and harms" of oral dosing of folic acid with or without vitamins B_6 and B_{12}. Studies that reported 100 patient-years of follow-up or less were excluded from the review (Koyama et al. 2002). In 4 randomized controlled studies, cardiovascular mortality was assessed in a total of 1186 participants and the relative risk was 0.93 with a 95% confidence interval of 0.70 to 1.22. Comparisons were made between high and low dose groups or between active and placebo treatments. The review concluded that the "homocysteine lowering therapies" studied were not found to reduce mortality (cardiovascular or all-cause) or cardiovascular events among people

with ESRD. Acknowledging the absence of evidence of effect on cardiovascular clinical outcomes, the National Kidney Foundation's 2020 Clinical Practice Guidelines for Nutrition in CKD provides the following information:[15]

> 5.1 Statements on Folic Acid
>
> Folic Acid Supplementation for Hyperhomocysteinemia
> 5.1.1 In adults with CKD 3-5D or posttransplantation who have hyperhomocysteinemia associated with kidney disease, we recommend not to routinely supplement folate with or without B-complex since there is no evidence demonstrating reduction in adverse cardiovascular outcomes (1A).
>
> Folic Acid Supplementation for Folic Acid Deficiency and Insufficiency
> 5.1.2 In adults with CKD 1-5D (2B) or posttransplantation (OPINION), we suggest prescribing folate, vitamin B12, and/or B-complex supplement to correct for folate or vitamin B12 deficiency/insufficiency based on clinical signs and symptoms (2B).

The guidelines describe folic acid products for these uses as "over-the-counter nutritional supplements," presumably oral products. There is no specific mention of the use of methylcobalamin.

(2) Hyperhomocysteinemia is a serious disorder. Research has suggested that it may be linked to fatal cardiovascular events in some populations, particularly those with cardiovascular disease. However, this has not been definitively established, nor has the impact of treatment on changing cardiovascular risk. Lowering of homocysteine levels appears most closely associated with the reduction of the occurrence of stroke.

(3) Hyperhomocysteinemia is treated with folate supplementation. Vitamin B_{12} and vitamin B_6 may be used concurrently.

Conclusions: No specific data were identified to support the effectiveness of methylcobalamin to treat hyperhomocysteinemia.

4. Autism Spectrum Disorder

(1) Four published clinical studies were found that examine the effectiveness of methylcobalamin in the treatment of autism or autism spectrum disorder. Anecdotal effectiveness of methylcobalamin to improve language in a child diagnosed with autism was described by Neurbrander (2005). The author credited subcutaneous injections of compounded methylcobalamin solution. Frye and Rossignol (2014) propose a theoretical basis for ASD based on mitochondrial dysfunction and abnormal folate, redox and tetrahydrobiopterin metabolism. Several clinical investigations attempted to find a clinical relationship to these theoretical pathophysiologic explanations for ASD.

[15] Available at: https://www.ajkd.org/article/S0272-6386(20)30726-5/fulltext

James et al. (2009) describes an uncontrolled, open-label trial of children age 2 to 7 years with "autistic disorder" treated for 3 months with both 75 µg/kg of methylcobalamin administered twice weekly via subcutaneous injection and 400 µg of oral folinic acid twice a day. Of the 48 children who enrolled in the trial, 40 completed. The purpose of the trial was to determine whether treatment with methylcobalamin and folinic acid would improve glutathione redox status (ratio of reduced to oxidized glutathione [GSH/GSSG]) and methylation capacity (ratio of SAM to S-adenosylhomocysteine [SAH]) in children with autistic disorder (James et al. 2004, James et al. 2006). The authors theorize that nutritional intervention to affect changes in these various metabolites may be of clinical benefit. Behavioral outcomes were also assessed. The authors stated that the Vineland Adaptive Behavior Scale (VABS) scores were significantly improved after treatment while still significantly below standard normal scores. The authors acknowledged the potential role of parental expectation bias in reporting outcomes during an open-label study and did not present VABS results. This trial was registered at clinicaltrials.gov as NCT00692315.

In the double-blind, placebo-controlled, cross-over trial conducted by Bertoglio et. al. (2010), 30 children with autism ages 3 to 8 years participated. Patients received either 6 weeks of 64.5 µg/kg of methylcobalamin subcutaneously every 3 days followed by 6 weeks of subcutaneous placebo of equal volume, or 6 weeks of placebo followed by 6 weeks of methylcobalamin. The authors compared improvement in the clinician-rated Clinical Global Impression-Improvement (CGI-I) scale[16] between methylcobalamin treatment and placebo. They also assessed the effect of methylcobalamin treatment on patient "behavior" via several rating scales: Parent Interview for Autism-Clinical Version, Peabody Picture Vocabulary Test-Third Edition, Aberrant Behavior Checklist (ABC), MacArthur Communication Developmental Inventory, and Stanford Binet V Edition. No statistically significant differences between methylcobalamin and placebo-treated patients were observed on any of these measures. The authors describe a post-hoc analysis that identified a "responder" subgroup of nine patients with statistically significant improvement on the CGI-I and at least two other measures. The authors go on to describe statistically significant improvement in blood plasma levels of glutathione (GSH) and glutathione redox status from baseline to end of methylcobalamin treatment. Of note, these levels were also higher following placebo treatment, though not to the same degree as they were post-methylcobalamin. The authors do not describe how GSH and GSH/GSSG levels in the non-responder subgroup change over time, nor do they describe how the change over time compares in responders versus non-responders

In an uncontrolled, open-label trial conducted by Frye et al. (2013), 44 children (age range not specified, mean age 5.1 $\pm$ 1.4 years) with "autistic disorder" and abnormal glutathione and methylation metabolism were treated for 3 months with both 75 µg/kg of methylcobalamin subcutaneously twice weekly and 400 µg of folinic acid orally twice a day. The reported data

[16] The reference provided by the authors for the CGI-I is: Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville, MD: US Department of Health, Education and Welfare, 1976. The manual can be found at: https://archive.org/details/ecdeuassessmentm1933guyw/page/4/mode/2up?ref=ol&view=theater The CGI-I is comprised of 3 items. Severity of illness is rated on a scale of 0 – 7; global improvement is rated on a scale of 0 – 7 and therapeutic effect of the "drug effect only" is rated "unchanged or worse," "minimal," "moderate" or "marked".

indicate that the 37 patients who completed the trial experienced improvement on the VABS over the course of the study. In addition, greater improvement in VABS scores was correlated with greater improvement in glutathione redox status. However, the authors do not state how end-of-treatment VABS scores compare to established norms and as an uncontrolled trial there is no comparator with which to assess contribution of the treatment to changes in the behavioral scores. In a subsequent publication that elaborates on the theoretical basis for nutritional supplementation with methylcobalamin and other substances, Frye and Rossignol (2014) conclude:

> Further research is needed to define subgroups of children with ASD in which these treatments may be most effective as well as confirm their efficacy in double blind placebo controlled, large-scale multicenter studies.

Hendren et al. (2016) conducted an 8-week, double-blind, placebo-controlled trial in 57 children ages 3 to 7 years with ASD. The effect of subcutaneous administration every three days of methylcobalamin 75 µg/kg was compared to saline placebo doses of identical volume. Patients in the methylcobalamin group experienced statistically greater improvement as measured by the clinician-rated CGI-I (placebo-subtracted improvement of 0.7 points on a 7-point scale). Clinical improvement among children treated with methylcobalamin was positively correlated with increases in plasma methionine ($p = 0.05$), decreases in SAH ($p = 0.007$) and improvements in the ratio of SAM to SAH ($p = 0.007$); the authors hypothesize that this indicates an improvement in cellular methylation capacity. No improvements were observed in the parent-rated ABC or the Social Responsiveness Scale (SRS).

A study report of 1257 mother-child pairs conducted at the Boston Medical Center prospectively showed an association between both low and high maternal intake of folate and vitamin B_{12} and increased risk of autism (Ragahavan et al 2018). Very high vitamin B_{12} (≥536.8 pmol/L) in mothers 2 to 3 days after birth were associated with a 2.5 times increase in risk (95% CI 1.4 4.5) of a child with autism. These results appear to be inconsistent with the theory that ASD should be treated with vitamin B_{12}. However, there remains a need to conduct further research to understand the complexity of this and many other genetic and environmental factors in the causation and treatment of ASD.

Johns Hopkins University Center for Excellence in Regulatory Science and Innovation (JHU CERSI) conducted an "Evaluation of Bulk Drug Substances Used to Compound Drug Products For Patients with Autism Spectrum Disorder (ASD): Phase II, Review of Available Evidence of Safety and Effectiveness And Evaluation of Current and Historical Use" (JHU CERSI 2020). See additional information about the JHU CERSI 2020 report in Section II.D. The two studies referred to in the JHU CERSI 2020 report have been discussed in this review, Bertoglio et al. (2010) and Hendren et al. (2016). Three Key Opinion Leaders (KOLs), expert practitioners in the ASD field, were interviewed about the potential for therapeutic benefit of various substances. Text on the following page has been extracted from JHU CERSI report regarding methylcobalamin.

Our systematic review identified two human studies (One trial with low risk of bias, one cross-over study with high risk of bias) but evidence was insufficient to draw conclusions.

Of the six compounds of interest evaluated, methylcobalamin (B12) was the second most commonly used (among the substances evaluated) in children with ASD (range in samples of 1% to 6%). Key Opinion Leaders (KOLs) noted that B12 would likely have no effect unless specifically taken to address a dietary deficiency.

(2) ASD is a serious disease. It is a neurodevelopmental disorder characterized by difficulties in social interaction, verbal and nonverbal communication, and repetitive behaviors. It may be associated with intellectual disability, sleep disturbance, seizures, gastrointestinal disorders, and other conditions. Symptoms begin in infancy and persist through the lifespan. ASD is characterized as a "pervasive" developmental disorder because multiple areas of development are delayed and the symptoms impact many functional domains. Avoidant - restrictive food intake disorder is a common cormorbidity among ASD patients can result in vitamin deficiencies (Bourne et al. 2017).

(3) Aripiprazole and risperidone are approved for the treatment of irritability associated with autism. Intensive behavioral interventions are the mainstay of ASD treatment.

Conclusions: Based on an extensive literature and internet search, there is negligible evidence that methylcobalamin is effective for the treatment of any aspect of ASD, aside from treatment of dietary insufficiency or other cobalamin-related disorder in patients who also have ASD. Among the studies reviewed here, the James and Frye trials were open-label trials; without a comparator, one cannot determine how much, if any, of the improvement on the VABS was due to the effect of the treatment or other factors. The Bertoglio trial was small and failed to show an effect of methylcobalamin. In the Hendren trial, the authors report a statistically significant difference on CGI-I with greater improvement noted for patients who received methylcobalamin treatment for 8 weeks. However, patients taking methylcobalamin improved only 0.7 points on the CGI-I, which is less than the 1 point typically regarded as a minimally clinically meaningful change. The CGI-I is a non-specific global measure of improvement; on scales that measure more specific symptoms (ABC, SRS), methylcobalamin was no better than placebo.

The main goal of the James et al. (2009) trial was to measure the effects of methylcobalamin on plasma levels of various metabolites. In each of the other cited publications, the authors provide exploratory analyses in attempts to either identify subsets of patients who might respond to methylcobalamin or to explore the potential mechanisms by which methylcobalamin might exert its effect on ASD symptoms. In some cases, the authors identify "statistically significant" differences between methylcobalamin treated patients and those in the placebo group. However, these few "positive" results were obtained without pre-specification and without adjustment for multiple comparisons. In light of these concerns, the "positive" results in the secondary analyses can be viewed as exploratory at best and require replication.

5. Amyotrophic lateral sclerosis

(1) Amyotrophic lateral sclerosis (ALS) is a progressive degeneration of upper and lower motor neurons resulting in progressive weakness in voluntary muscles and eventually muscles of respiration. Treatment includes supportive physical equipment, feeding tubes and respiratory equipment (Miller et al. 2009).

In 2016, Blasco et al. reviewed therapies being investigated for "a family of age-related neurodegenerative disorders" termed amyotrophic lateral sclerosis (ALS). The authors identified that there are many ongoing research tracks for ALS treatment, but negative trials are common in the evaluation of ALS drug treatments in part because the disease is "rare, heterogeneous and rapidly progressive." For methylcobalamin, a phase II/III study of ultra-high dose methylcobalamin was conducted in Japan (ClinicalTrials.gov ID: NCT0044613) based on two preliminary studies (Kaji et al. 1998, Kaji et al. 2019). Doses of 25 or 50 mg methylcobalamin or placebo were given by intramuscular injection twice a week over 3.5 years in 373 patients. Per an English abstract, no differences were found between treated and untreated patients except that treated patients' survival was improved in a post-hoc analysis of patients enrolled within one year of diagnosis. Based on this limited evidence of effect, a second, similar trial has been conducted in Japan (ClinicalTrials.gov ID: NCT00445172). Oki et al. (2018) describes the study protocol. Although the investigators expected to publish their results by March 2020, no related publications have been identified as of the date of this review.

(2) ALS is a fatal disease with median life expectancy of 3 years from onset (Chio et al. 2009).

(3) There are two FDA approved drugs to slow the progression of ALS. Riluzole was approved by FDA in 1995 as an oral tablet indicated to treat ALS. Oral liquids and an oral film were subsequently approved. In clinical trials, riluzole acted to increase time before patients required a tracheostomy or died, as compared to placebo. Muscle strength and neurological function did not show a benefit, per the FDA approved riluzole ANDA label.[17] Edaravone was approved in 2017 as an intravenous injection, also indicated for the treatment of ALS. Clinical trials established that it slowed progression of symptoms over 24 weeks compared to placebo.[18] The combination of dextromethorphan hydrobromide and quinidine sulfate is approved to treat pseudobulbar affect, which may occur in ALS patients.[19]

Conclusions: We were unable to identify any studies that show methylcobalamin is effective in the treatment of ALS.

6. Peripheral Neuropathy

(1) Peripheral neuropathies are a range of disorders, the most common being distal sensory polyneuropathy (Barrell and Smith 2018). Peripheral nerve injury is most commonly caused by diabetes, accounting for 50% of cases. It occurs in approximately half of patients with diabetes (Iqbal et al. 2018). The second most common cause, accounting for 40% of cases, is idiopathic

[17] Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020599s017lbl.pdf
[18] Accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209176s009lbl.pdf
[19] Accessible at: https://www.nuedexta.com/sites/default/files/2020-04/Prescribing_Information.pdf

polyneuropathy. It is diagnosed based on excluding other diagnosis and is associated with an increased risk of prediabetes and metabolic syndrome. Toxins and medications, such as metformin and chemotherapy drugs, are associated also with the development of peripheral neuropathy. Vitamin B_{12} deficiency due to insufficient dietary intake or absorption issues (e.g. pernicious anemia) can cause peripheral neuropathy that includes spinal cord involvement, so correction of such deficiency is necessary. These disorders are associated with a wide range of symptoms, such as burning, tingling, pins-and-needles, electric shocks, hyperalgesia (increased sensitivity to painful stimuli) or allodynia (painful sensation to innocuous stimuli), as well as changes in nerve conduction parameters, neuropathological lesions and quality of life issues (Stino and Smith 2017).

- Diabetic periphernal neuropathy

Diabetic neuropathy is thought to be a "multi-factorial metabolic process that increasingly deteriorates tissues" caused by: hyperglycemia and advanced glycated end products, increased sorbitol and protein kinase C, elevated homocysteine, reduced nitric oxide and excessive reactive oxygen species (Miranda-Massari et al. 2011). These factors damage endothelial tissues, increase vascular resistance, and reduce blood flow to nerves. A 2005 review of the effectiveness of vitamin B_{12} on diabetic neuropathy Sun et al. (2005) identified 3 randomized, controlled trials in which methylcobalamin treatment was studied and several more studies in which vitamin B_{12} was the active treatment. The authors concluded that the variability of outcomes, both sensory and electrophysiologic, was considerable and the effects of methylcobalamin administration (intravenous or oral) on the diabetic neuropathy signs and symptoms may be a result of correcting underlying deficiency (e.g., from metformin administration). Overall, it was suggested that high-quality, double-blind randomized controlled trials are needed to confirm the clinical effectiveness of vitamin B_{12} or methylcobalamin.

One study of methylcobalamin from the Sun et al. (2005) review is recurrently cited in the literature (Yaqub et al. 1992). Fifty diabetic patients were randomized to receive placebo or 500 mg methylcobalamin 3 times daily for four months. A peripheral neuropathy scoring system was developed to include evaluation of somatic symptoms, autonomic symptoms and clinical signs. It is unclear whether the patient or physician completed the assessment. Scores were compared within, rather than between, groups at the start of the study and after 4 months, so no conclusions can be drawn with respect to the treatment differences. The study is, however, often cited as demonstrating methylcobalamin efficacy, on sensory but not on neurophysiologic endpoints. Studies of methylcobalamin and other substances such as alpha lipoic acid (Han et al. 2018), acetyl-l-carnitine (Li et al. 2016) and pregabalin (Vasudevan et al. 2014) have been conducted without methylcobalamin only treatment arms or without placebo controls, providing negligible information on which to determine methylcobalamin's activity.

On following page is an excerpt from the American Diabetes Association's "Standards of Medical Care in Diabetes – 2021" regarding diabetes related neuropathy. Methylcobalamin treatment is not identified as a standard of care.[20]

[20] Available at: https://clinical.diabetesjournals.org/content/39/1/14

Neuropathy

Recommendations

Screening

- **11.25** All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- **11.26** Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**
- **11.27** Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

Treatment

- **11.28** Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **A** and to slow the progression of neuropathy in patients with type 2 diabetes. **B**
- **11.29** Assess and treat patients to reduce pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**
- **11.30** Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

- Uremic-diabetic polyneuropathy

Uremic-diabetic polyneuropathy is a term adopted in the 1960s for signs and symptoms that were present in diabetic and other patients with chronic renal failure (Asbury 1963). Currently, early implementation of dialysis and improved methods of dialysis and transplantation have considerably lowered the occurrence of uremic neuropathy (Said 2013). In an uncontrolled study, nine patients receiving maintenance hemodialysis were given 500 μg of methylcobalamin (from Eisai Co Ltd in Japan) intravenously 3 times a week for 6 months (Kuwabara et al. 1999). Patients were heterogeneous in that the cause of renal failure was chronic glomerulonephritis (n = 5), diabetes mellitus (n = 6) and renal tuberculosis (n = 1), there were 4 men and 5 women, ages ranged from 48 to 72 years, and duration of hemodialysis was between 2 and 20 years. All patients were uremic and 4 patients were also diabetic. At the end of the six months of treatment, neuropathic pain or paresthesia grading had declined from 1.8 to 1.4 (scale of 0 to 3), but in two patients (not identified further) the pain grade remained unchanged. Two of 18 nerve conduction parameters (ulnar motor conduction velocity and medial sensory conduction velocity) were statistically significantly increased only in upper limb nerves. The authors note that placebo effects could not be ruled out in the uncontrolled study but that "in Japan methylcobalamin is widely used to treat various neuropathies." No larger studies or placebo controlled studies of methylcobalamin treatment for uremic-diabetic polyneuropathy were found.

- Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy has been associated with advanced malignancy in which methylcobalamin levels decrease rapidly, in comparison to the development of dietary deficiency, during chemotherapy exposure (Solomon 2016). This functional deficiency may be a major causal factor in the development of the associated neuropathy. Schloss and Colosimo (2017) reviewed the published literature identifying 5 studies and 1 case report assessing the use of methylcobalamin or B complex vitamins in chemotherapy-induced peripheral neuropathy. One study was randomized and placebo controlled with a total of 47 patients eligible for analysis (Schloss et al. 2017). No statistically significant difference was found between active and placebo groups on a total neuropathy score including signs and symptoms assessed by an independent neurologist. However, patients taking the B complex perceived a reduction in sensory peripheral neuropathy and investigators suggest that a more "robust" clinical study may show reduction in onset and severity.

- Chronic idiopathic axonal polyneuropathy (CIAP)

Chronic idiopathic axonal polyneuropathy (CIAP) is a condition with onset of numbness or pain, usually in patients over the age of 60, with slow or no progression and no other causal explanation (Zis et al. 2019). A current review of drug therapy for CIAP found that no adequately controlled clinical studies have been published (Warnedorf et al. 2017). Treatment is generally symptomatic including pain therapies and antidepressants. (Zis et al. 2016). No data for methylcobalamin use in CIAP were identified.

(2) Diabetic, uremic, chemotherapy-induced and CIAP peripheral neuropathies are serious disorders in that they introduce considerable sensory and motor challenges and may reduce quality of life. They are not life threatening disorders.

(3) Oral tapentadol hydrochloride and duloxetine hydrochloride are FDA approved for treatment of diabetic peripheral neuropathy. Oral pregabalin and topical capcaisin patches are FDA approved for the treatment of diabetic peripheral neuropathy and post herpetic neuralgia. Other FDA approved medications with a general pain indication may also be used to treat pain associated with peripheral neuropathies. Anticonvulsants and serotonin-norepinephrine reuptake inhibitors are also used in clinical practice for symptomatic treatment. Physiotherapy is often implemented to further reduce symptoms.

Conclusions: Available data do not support the effectiveness of methylcobalamin in the treatment of diabetic peripheral neuropathy, uremic-diabetic polyneuropathy, chemotherapy-induced peripheral neuropathy or CIAP peripheral neuropathy.

7. Pain Management

(1) Methylcobalamin has been investigated for use in the treatment of pain. Zhang et al. (2013) identified clinical studies in which the effect of methylcobalamin as a single treatment was assessed.

Herpetic neuralgia - In one study, patients who had been diagnosed with unilateral, dermatomal pain related to herpes zoster on the torso lasting for 30 days or more after onset of rash and less than 120 days onset of vesicles were enrolled to receive local subcutaneous methylcobalamin injections (n = 33), oral methylcobalamin (n = 33) or 1% subcutaneous lidocaine injections (n = 32) daily for 28 days (Xu et al. 2013). Although numerical trends and some statistical analyses of pain rating and quality of life endpoints favored methylcobalamin injections over the other two treatments, lack of a placebo comparator, particularly a placebo injection, compromises the interpretability of this study. Other factors potentially confounding the interpretation of treatment effectiveness were that blinding of patients and administering physicians was not possible due to the color of the injectables, patients had treatment with oral acyclovir for 7 days at the onset of the rash and patients were allowed to continue oral analgesics throughout the study. The authors state that their findings should be confirmed through additional studies. It is also noted that in future studies, inclusion of patients diagnosed as having postherpetic neuropathy should be considered as there are FDA approved products indicated for this disorder.

Lumbar spinal stenosis – Tran et al. (2010) reviewed the published literature for nonsurgical management of pain and functionality associated with lumbar spinal stenosis, identifying one study of treatment with methylcobalamin. Waikakul and Waikakul (2000) randomized 152 patients to receive either standard care (oral analgesics, physiotherapy, etc.) or standard care plus 0.5 mg oral methylcobalamin 3 times a day for 6 months. No intergroup differences were seen in terms of pain or other neurological findings, with the exception of a numerically greater improvement in ambulation within the methylcobalamin group at assessment timepoints throughout the study.

Low back pain – In a double-blind, randomized, placebo-controlled trial, 60 patients were randomized to receive 6 intramuscular injections during a two week period of methylcobalamin 1000 μg or placebo (Chiu et al. 2011). Statistical analysis of ratings on a disability index and pain score visual analog scale were reported only based on within-group changes. Numerical trends favored methylcobalamin for reported endpoints. Patients were allowed to use up to 3 gm of acetaminophen per day and the one published inter-group analysis showed significantly lower acetaminophen use among methylcobalamin recipients (87.6 g versus 65.7 g, p = 0.04).

(2) Pain associated with herpetic neuralgia and lumbar spinal stenosis, and chronic nonspecific lower back pain, can introduce substantial functional and quality of life limitations but none of these conditions are life threatening.

(3) Numerous topical, oral and injectable medications are FDA approved to treat pain, and physiotherapy is often implemented to further reduce symptoms.

Conclusions: Available data do not support methylcobalamin's effectiveness in the treatment of pain.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on methylcobalamin in regard to Section II.D of this consultation included PubMed, ClinicalTrials.gov, compoundingtoday.com, Natural Medicines Database, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, USP/NF, and Google.

FDA requested current and historical use information for methylcobalamin from the University of Maryland Center of Excellence in Regulatory Science and Innovation (UMD CERSI) and JHU CERSI, as previously discussed. This section references information from both reports

1. Length of time the substance has been used in pharmacy compounding

The nominator did not provide historical use data. In 1962, Guest et al. discovered a methyl analogue of cobamide coenzyme and termed this analogue 'methylcobalamin' (Guest et al, 1962). There is insufficient literature evidence available to determine the length of time methylcobalamin has been used in pharmacy compounding. The earliest literature found that mentions compounding methylcobalamin in the United States is from 2005 and describes the author's success with using compounded preparations in the treatment of patients with autism (Neubrander, 2005).

2. The medical condition(s) it has been used to treat

No compounded drug products containing methylcobalamin were identified from any studies reviewed as part of the UMD CERSI report (UMD CERSI 2020).[21] However, from the literature review conducted, the most common uses of methylcobalamin in both the US and non-US studies were diabetic peripheral neuropathy and hyperhomocysteinemia. From a survey of 27 healthcare practitioners (Doctor of Medicine, Naturopathic Doctor, Doctor of Osteopathic Medicine), ten practitioners reported using, prescribing, or recommending multiple types of methylcobalamin products. Five out of the ten practitioners reported having used, prescribed, or recommended compounded methylcobalamin. One practitioner out of the five reported purchasing compounded office stock methylcobalamin from a compounding pharmacy for reasons of convenience. The most common reported use of compounded methylcobalamin was for fatigue. According to the respondents, uses for which compounded methylcobalamin is considered a standard therapy include anemia, autism, back pain, muscle cramps, fatigue, neuropathy, vitamin B_{12} deficiency and weight loss. Bioavailability and quality were the reasons for using the compounded methylcobalamin drug product over an FDA-approved drug product.

Limitations of the UMD-CERSI study include bias with self-reporting and the limited number of health practitioners surveyed, per FDA assessment. The databases that were surveyed encompass specific subpopulations and may not be representative of methylcobalamin use in the

[21] Available at: https://archive.hshsl.umaryland.edu/bitstream/handle/10713/12216/Methylcobalamin_Final_2020_02.pdf?sequence=6&isAllowed=y

general population. The UMD-CERSI study is one source of information that we considered among many.

Results from a Google search using the terms *methylcobalamin compounding pharmacy* indicate that methylcobalamin is/has been compounded as an intramuscular and subcutaneous injection, transdermal gel, sublingual drop, sublingual tablet, capsules, lozenges, oral spray, nasal spray and buccal, sublingual or chewable "nugget." It is often advertised as the "active" form of vitamin B_{12}, although the exogenous form is not active, as previously explained.

Table 6. Additional Conditions found in Compounding Pharmacy Advertisements for the use of Methylcobalamin

Treatment of:	• Fibromyalgia
Helps in improving:	• Immunity • Decay of aging at the cellular level • Memory and concentration • Energy • Heart disease • Mood • Stress
Beneficial for patients with:	• Anorexia • Nausea • Vomiting • Diarrhea • Headache • Circadian rhythm sleep disorders • Depression • Fatigue • AIDS • Inflammatory bowel disease (IBD) • Lyme disease • Osteoporosis • Tendonitis • Psychiatric disorders • Alzheimer's disease • Liver • Kidney disease • Asthma

There are weight loss clinics in the U.S. that offer methylcobalamin injections as a part of their weight loss programs,[22] claiming that it improves metabolism, increases energy, and improves the quality of sleep. It appears that methylcobalamin is used alone or in combination with other

[22] For example, see https://theaspenclinic.com/aspen-clinic-program/injections/ and https://www.defymedical.com/home/weight-management-overview/.

so called "lipotropic" ingredients (e.g. methionine, inositol, choline) as an injection.[23]
In addition, several "IV clinics" or "hydration clinics" offer methylcobalamin as a component of their intravenous infusions.[24] For example, methylcobalamin, in combination with several other ingredients, is included in an infusion to "help reverse the symptoms of alcohol intoxication and toxicity through intravenous (IV) replenishment of nutrients."[25] We do not have information on the range of doses being administered to patients for the different conditions.

3. *How widespread its use has been*

The JHU CERSI report evaluated the current and historical use of six bulk drug substances (inositol, 2,3-Dimercapto-1-propanesulfonic acid, glutathione, melatonin, oxytocin and methylcobalamin) for use in autism spectrum disorder (JHU CERSI 2020). The report drew on three distinct data resources for estimates of use: a clinical sample, population sample, and national sample. Interviews of key opinion leaders in research and practice were previously discussed.

Use of Methylcobalamin in a Clinical Sample: In a clinical sample of 1,788 children with ASD under 17 years of age that receive care at Kennedy Krieger Institute Center for Autism and Related Disorders, <1% used vitamin B_{12} orally administered.

Use of Methylcobalamin in a Population Sample: In a population of 1,487 parents of children under 18 years of age from the Simons Foundation Powering Autism Research through Knowledge initiative, an online registry of self-referred parents/caregivers of individuals with autism, vitamin B_{12} substances (6.0% methylcobalamin, 5.5% B complex) were the second most frequently used of the six substances studied. Notably, respondents reported that methylcobalamin was administered to address difficulties with language and communication and it was most frequently administered orally.

Use of Methylcobalamin in a National Sample: Evaluation of Medicaid claims data from the years 2010-2014 for children with or without ASD revealed that of the medications assessed, "B12" was the most frequently used although the percent of users observed was still low (1.1% among Medicaid enrolled children with ASD). Injection and solution were the most common forms of "B12" prescription. However, the report was unclear regarding which cobalamins "B12" refers to. There was also little indication of increased use among children with ASD, compared to children without ASD, in this sample.

Per JHU-CERSI, some limitations of the study include recall bias with self-reporting, CMS data not capturing drug utilization paid for by non-Medicaid means and limited number of KOLs interviewed. The JHU-CERSI study is one source of information that we considered among many.

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[23] For example, see http://www.pharmacyrxsolutions.com/mic-plus-injections.cfm and https://www.defymedicalstore.com/978-emp.
[24] For example, see https://eghealthcare.net/integrative-medicine/iv-infusions/formulas/ and https://www.defymedicalstore.com/in-office-procedures.
[25] See https://www.defymedicalstore.com/170.

The International Journal of Pharmaceutical Compounding (IJPC) has published compounding formulations for methylcobalamin 20 mg [vitamin B12] sublingual troche[26], methylcobalamin 3000 µg/mL [vitamin B12] sublingual liquid,[27] methylcobalamin 25 µg/mL [vitamin B12] sterile intramuscular injection,[28] methylcobalamin 25 µg/mL [vitamin B12] in sodium chloride 0.9% sterile intramuscular injection[29] and choline 1.6%, chromic [chromium] chloride 0.03%, inositol 1.6%, methionine 0.8% and methylcobalamin 0.0001% sterile injection, preserved.[30]

4. Recognition of the substance in other countries or foreign pharmacopeias

Mecobalamin (alternate name for methylcobalamin) is approved in Japan as 250 µg and 500 µg tablets and 0.1% granules for the treatment of peripheral neuropathies (Product Insert 2014; Integrated Report 2020). In addition, mecobalamin is approved as a 500 µg/1 mL injection for the treatment of peripheral neuropathies and megaloblastic anemia caused by vitamin B_{12} deficiency (Product Insert 2004). According to the sponsor's website, mecobalamin was launched in Japan in 1978.[31]

Mecobalamin is also approved in China for the treatment of peripheral neuropathies (Integrated Report 2016; Amerigen Announcement 2014).

Mecobalamin is listed in the Japanese Pharmacopoeia (17th Edition).[32] A search of the British Pharmacopoeia (BP 2020)[33] and the European Pharmacopoeia (10th Edition, 10.3)[34] did not show any listings for methylcobalamin or mecobalamin.

Methylcobalamin 5mg/mL intramuscular injection is approved in Australia for the treatment of pernicious anemia and peripheral and diabetic neuropathies (Consumer Medicine Information Leaflet 2017, Therapeutic Goods Administration).

According to the UM CERSI report, mecobalamin 0.5mg/mL injection was approved in Hong Kong in 1992

Conclusions: Based on internet searches, it appears that compounding pharmacies in the U.S. have been preparing methylcobalamin as an intramuscular and subcutaneous injection, intravenous infusion, transdermal gel, sublingual drop, sublingual tablet, capsules, lozenges, oral spray, nasal spray and buccal, sublingual and chewable "nugget" for the treatment of pernicious anemia, vitamin B_{12} deficiency, peripheral and diabetic neuropathies, fibromyalgia and autism,

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[26] Available at: https://compoundingtoday.com/Formulation/FormulaInfo.cfm?ID=2000 (subscription required)
[27] Available at: https://compoundingtoday.com/Formulation/FormulaInfo.cfm?ID=2652 (subscription required)
[28] Available at: https://compoundingtoday.com/Formulation/FormulaInfo.cfm?ID=2979 (subscription required)
[29] Available at: https://compoundingtoday.com/Formulation/FormulaInfo.cfm?ID=2981 (subscription required)
[30] Available at: https://compoundingtoday.com/Formulation/FormulaInfo.cfm?ID=2304 (subscription required). While the formula does not include information on the medical condition the product is intended to treat, the formula page includes a "use" section which states, "The lipotropic weight loss injection is one approach to weight loss which may be customized for the need of the patient. The ordering physician should specify the strength of each component."
[31] Available at: http://www.eisai.com/company/profile/history/.
[32] Available at: https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[33] Available at: https://www.pharmacopoeia.com/
[34] Available at: https://pheur.edqm.eu/app/10-3/search/ (subscription required)

among other conditions. According to the JHU CERSI report that evaluated six substances used for ASD, compounded vitamin B_{12} is infrequently used as a treatment for ASD in the U.S.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate methylcobalamin for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** placing methylcobalamin on that list based on the following:

1. Methylcobalamin is physically and chemically well characterized. It is likely to be stable when compounded as solid and liquid formulations under ordinary storage conditions with protection from light and proper formulation techniques, such as controlled pH and temperature.

2. Methylcobalamin is found in food and is a dietary ingredient in dietary supplements, so exposure from oral ingestion appears to be safe. However, the safety of methylcobalamin administration by intramuscular, subcutaneous or intravenous injections or infusions for a wide variety of uses, as currently promoted online by clinics and compounding pharmacies, is not supported by adequate data.

3. The pharmacologic mechanism of methylcobalamin suggests that it is likely to be effective in treating vitamin B_{12} deficiency. Although no U.S. clinical studies of methylcobalamin to treat vitamin B_{12} deficiency were found, non-U.S. studies support this use. No studies have been identified that compare the effectiveness of methylcobalamin to treat vitamin B_{12} deficiency relative to other cobalamins, and we found no data regarding clinical situations in which FDA approved hydroxocobalamin or cyanocobalamin are insufficient to provide treatment. Hydroxocobalamin and cyanocobalamin are used in the U.S. to treat certain inborn errors of metabolism of cobalamin absorption, transport or activity. No specific information was found that supports the effectiveness of methylcobalamin to treat inborn errors of metabolism. Regarding other conditions proposed to be treated with methylcobalamin in the nominations, including hyperhomocysteinemia, ASD, ALS, peripheral neuropathy, and pain, negligible or no specific data were identified to support the effectiveness of methylcobalamin to treat these conditions.

4. Methylcobalamin has been used in pharmacy compounding since at least 2005 and has been compounded in a variety of dosage forms and routes of administration for the treatment of a wide range of serious conditions. In addition to the nominated uses, methylcobalamin is also reportedly administered by injection or infusion treatments for weight loss, hydration, and a variety of serious conditions as promoted on the websites of compounding pharmacies.

Methylcobalamin is a vitamer of vitamin B_{12} and based upon the use of other cobalamins would be expected to be effective in treating vitamin B_{12} deficiency. However, it is not clear that treatment of vitamin B_{12} deficiency is currently the primary use of compounded methylcobalamin in the U.S. or that methylcobalamin provides a unique benefit over other

vitamers of vitamin B_{12} that are available in FDA approved drug products. It appears that the primary use of compounded methylcobalamin is to treat patients with conditions, in some cases serious, for which there is little evidence to support the effectiveness. We do not have information on the range of doses or the frequency of administration and cannot make a judgement on the safety of the current use of injectable products in patients.

Based on the information the Agency has considered in balancing the four evaluation factors, the lack of effectiveness data and safety data for use of injectable products in patients ***weighs against*** methylcobalamin being added to the 503A Bulks List.

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APPENDIX 1: Activated Methylcobalamin and Activated Adenosylcobalamin Activity

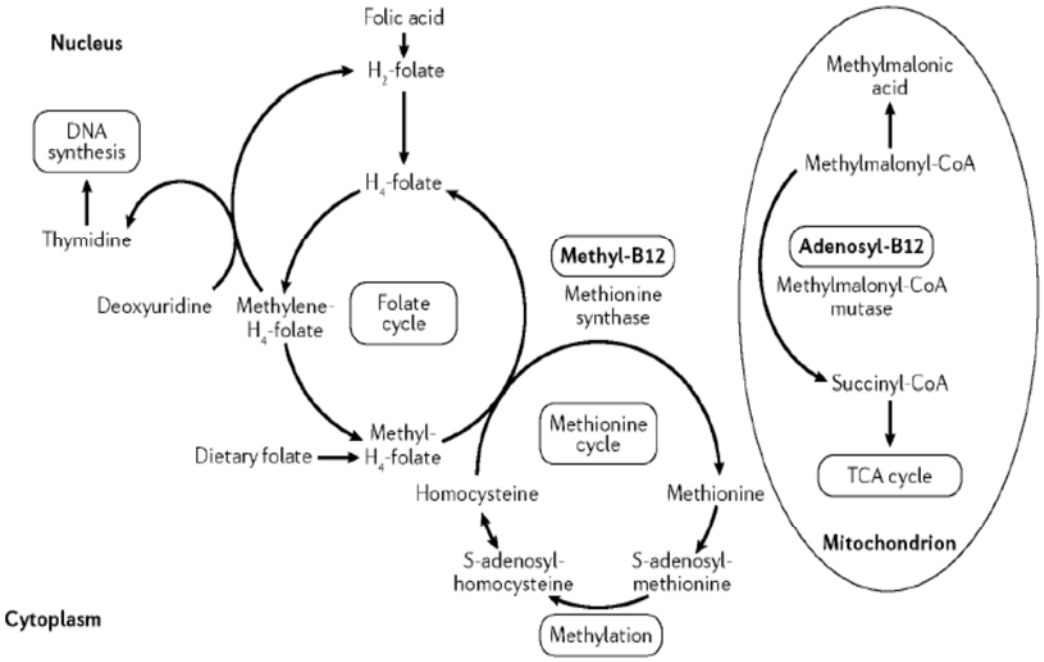

Figure 1 | **Vitamin B_{12} and folate metabolism and function.** Vitamin B_{12} (B12) and folate are required for the methionine synthase reaction in which a methyl group is transferred from methyltetrahydrofolate (methyl-H_4-folate; also known as levomefolic acid) to homocysteine by methionine synthase, with methyl-B12 as a coenzyme to form methionine. The resulting H_4-folate can then be returned to the folate pool and made available for the generation of methylene-H_4-folate, the form required for *de novo* synthesis of thymidine, which is essential for DNA replication and repair. Hence, either folate or B12 deficiency results in the same biochemical perturbation in thymidine synthesis and DNA replication. In the case of B12 deficiency, folate is 'trapped' in the unusable methyl-form[5,194]. B12 is also involved in the conversion of methylmalonyl-CoA (methylmalonic acid bound to coenzyme A) to succinyl-CoA by the enzyme methylmalonyl-CoA mutase with adenosyl-B12 as a cofactor; succinyl-CoA is a major intermediary of the tricarboxylic acid (TCA) cycle. In B12 deficiency, substrates of both B12-dependent reactions accumulate, which leads to increased levels of methylmalonic acid and homocysteine in the plasma. A combination of low levels of B12 and increased levels of folate was associated with higher concentrations of methylmalonic acid and total plasma homocysteine[156,157]. Major complications of B12 deficiency are megaloblastic anaemia, as a result of inhibition of DNA synthesis, and neurological manifestations.

APPENDIX 2: Huemer and Baumgartner 2019

TABLE 1 Overview of genetic and biochemical markers of nutritional, acquired and inborn Cbl-related disorders

Diseases/defects	Gene	Phenotype MIM number	MMA	tHcy	Met	Cbl[a]	Comments
Neonatal Cbl deficiency	—	—	↑	↑	↓/n	↓	• NBS: C3; C3/C2 often ↑ • Differentiate from inborn error of Cbl metabolism • Maternal nutrition or gastrointestinal disease?
Nutritional Cbl deficiency	—	—	↑	↑	↓/n	↓	• Exclude additional (eg, folate) deficiencies • Holo-TC rises with oral Cbl load • Differentiate from inborn errors of Cbl metabolism
Cbl deficiency due to IF/gastric parietal cell antibodies	—	—	↑	↑	↓/n	↓	• Prove antibody status • Comorbidities? • Holo-TC unchanged with oral Cbl load
Inborn errors of cobalamin absorption and systemic trafficking							
Gastric intrinsic factor deficiency	*GIF* 11q12.1	261000	↑	↑	↓/n	Often ↓	• No antibodies against IF/gastric parietal cells • Holo-TC unchanged with oral Cbl load • Holo-TC increase with parenteral Cbl load • Differentiate from other inborn errors of Cbl metabolism!
Imerslund-Gräsbeck syndrome	*AMN* 14q32.32 *CUBN* 10p13	261100	↑	↑	↓/n	Often ↓	• Proteinuria (~50%) • Holo-TC unchanged with oral Cbl load • Differentiate from other inborn errors of Cbl metabolism!
Transcobalamin deficiency	*TCN2* 22q12.2	275350	↑	↑	↓/n	n	• Holo-TC unchanged with oral or parenteral Cbl load • Differentiate from other inborn errors of Cbl metabolism
Haptocorrin deficiency	*TCN1* 11q12.1	—	n	n	n	↓	• Asymptomatic
Transcobalamin receptor	*CD320* 19p13.2	613646	Mild ↑	Mild ↑	?	n	• Pathogenicity unclear • Met not systematically documented, but probably normal • Differentiate from other inborn errors of Cbl metabolism
Inborn errors of intracellular cobalamin metabolism and trafficking							
cblA	*MMAA* 4q31.21	251100	↑	n	n	n	Isolated MMAurias: • Differentiate from Mut dysfunction • Differentiate between complementation groups (fibroblast complementation or genetic studies) • Test for Cbl responsiveness
cblB	*MMAB* 12q24.11	251110	↑	n	n	n	
cblD-MMA	*MMADHC* 2q23.2	277410	↑	n	n	n	
cblF	*LMBRD1* 6q13	277380	↑	↑	↓/n	n	Combined remethylation disorders: • Differentiate between complementation groups (fibroblast complementation or genetic studies) • Differentiate from acquired or nutritional Cbl deficiency and inborn errors of Cbl absorption
cblJ	*ABCD4* 14q24.3	614857	↑	↑	↓/n	n	
cblC	*MMACHC* 1p34.1	277400	↑	↑	↓/n	n	
cblD-MMAHcy	*MMADHC* 2q23.2	277410	↑	↑	↓/n	n	
cblD-Hcy	*MMADHC* 2q23.2	277410	n	↑	↓/n	n	Isolated Cbl-related remethylation disorders: • Exclude folate deficiency • Exclude MTHFR deficiency • Exclude other (eg, renal) diseases causing hyperhomocysteinemia • Differentiate between complementation groups (fibroblast complementation or genetic studies)
cblE	*MTRR* 5p15.31	236270	n	↑	↓/n	n	
cblG	*MTR* 1q43	250940	n	↑	↓/n	n	

TABLE 1 (Continued)

Diseases/defects	Gene	Phenotype MIM number	MMA	tHcy	Met	Cbl[a]	Comments
Inborn errors of folate metabolism affecting remethylation							
MTHFR deficiency	*MTHFR* 1p36.22	236250	n	↑	↓ or n		• 5-MTHF low in cerebrospinal fluid • Serum folate may be low • Differentiate from isolated Cbl-related remethylation disorders and MTHFD1 disease
MTHFD1 deficiency	*MTHFD1* 14q23.3	617780	n	↑/n	↓ or n		• Differentiate from isolated Cbl-related remethylation disorders and MTHFR deficiency

Abbreviations: Cbl, cobalamin; Hcy, homocysteine; Holo-TC, holotranscobalamin; Met, methionine; MMA, methylmalonic acid; MTHF, methylenetetrahydrofolate; MTHFD, methylenetetrahydrofolate dehydrogenase; MTHFR, methylene tetrahydrofolate reductase; Mut, methylmalonyl-CoA mutase; tHcy, total homocysteine.

[a]In inborn errors of Cbl metabolism, Cbl levels may be low due to unrelated reasons. Low Cbl does not by principle exclude an inborn error in the downstream pathway.

Tab 3

Choline Chloride

Tab 3a

Choline Chloride Nominations

Alliance for Natural Health USA
6931 Arlington Road, Suite 304
Bethesda, MD 20814

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
anhinternational.org

September 30, 2014

VIA ELECTRONIC SUBMISSION

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: "Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations" published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the "Agency").

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the "503A List"). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

As discussed in detail below, in the interest compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA's members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA's Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp.,[1] with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

[1] As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Choline chloride
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)? *Provide an explanation for why it is considered an active ingredient when it is used in specific compounding drug products, and provide citations to specific sources that describe its active properties.*	Yes. There is ample information in PubMed. Please access this article: J Nutr. 2013 Dec 24. [Epub ahead of print] Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL.
Is the ingredient listed in any of the three sections of the Orange Book?	Not for choline chloride
Were any monographs for the ingredient found in the USP or NF monographs?	Not for choline chloride
What is the chemical name of the substance?	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, chloride
What is the common name of the substance?	Choline chloride
Does the substance have a UNII Code?	45I14D8O27
What is the chemical grade of the substance?	USP Dietary monograph for this bulk drug substance available This material is FCC graded
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received Raw material is a generally recognized as safe (GRAS) dietary supplement. and can be supplied by a 510-FDA registered manufacturer
How is the ingredient supplied?	Choline chloride is a white to off white hygroscopic crystal.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 200-655-4). Canada: Listed on Canadian Domestic Substance List (DSL). China: Listed on National Inventory. Japan: Listed on National Inventory (ENCS). Korea: Listed on National Inventory (KECI). Philippines: Listed on National Inventory (PICCS). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	As a single API preparation or in a combination preparation from 25 mg/mL to 100 mg/mL, multiple dose or preservative free, in various sizes up to 30 mL. The proposed product will be compounded as a sterile injectable in various concentrations ranging from 25 mg/mL to 100 mg/mL, 30 mL multiple dose or preservative free vial, and an example formulation is below. Each mL contains: Choline chloride 50 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, in various concentrations and formulations containing Choline chloride and other vitamins, supplements and/or minerals, packaged in various sizes ranging from 10 mL to 30 mL, multiple dose vial, or preservative free vial. Some example formulations are below. Each mL contains: Inositol 50 mg Choline chloride 50 mg L-methionine 25 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous, intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. 2. J Biol Chem. 2013 Jan 11;288(2):837-47. doi: 10.1074/jbc.M112.415117. Epub 2012 Nov 25. Choline supplementation promotes hepatic insulin resistance in phosphatidylethanolamine N-methyltransferase-deficient mice via increased glucagon action. Wu G, Zhang L, Li T, Zuniga A, Lopaschuk GD, Li L, Jacobs RL, Vance DE. 3. Biochim Biophys Acta. 1997 Sep 4;1348(1-2):142-50. Phosphatidylethanolamine N-methyltransferase from liver. Vance DE, Walkey CJ, Cui Z. 4. PLoS One. 2014 Jan 15;9(1):e85848. doi: 10.1371/journal.pone.0085848. eCollection 2014. Lipid Metabolism, Oxidative Stress and Cell Death Are Regulated by PKC Delta in a Dietary Model of Nonalcoholic Steatohepatitis. Greene MW1, Burrington CM2, Lynch DT2, Davenport SK3, Johnson AK2, Horsman MJ2, Chowdhry S4, Zhang J5, Sparks JD6, Tirrell PC4. 5. Breast Cancer Res. 2014 Jan 21;16(1):R5. [Epub ahead of print] Interplay of choline metabolites and genes in patient-derived breast cancer xenografts.

Has the bulk drug substance been used previously to compound drug product(s)?	Yes. For many decades.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Supplementation as exogenous source of choline for metabolic pathways.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are no FDA-approved injectable products containing choline chloride as a single API or in a combination.
Is there any other relevant information?	Thousands of patients with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by integrative, alternative and naturopathic physicians daily. Chemically Choline chloride is as stable in aqueous solutions represented by commercial enteral products containing Choline chloride (and other vitamins and minerals) available and stable for at least 12 months. - Ensure® Nutrition Shake - PediaSure® (Retail) Vanilla - Boost® Original

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, "Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances" relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and

doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency's request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

Naturopathic Medicine and Naturopathic Physicians

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient's condition rather than focusing solely on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses, and order lab tests, imaging procedures, and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate.

NDs attend 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 such schools in North America. Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.

Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors, as well as compounding pharmacists, to ensure safe and comprehensive care.

Characteristics of Patients Seen by Naturopathic Physicians

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors' offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients' immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the 'multi-systems' approach of naturopathic medicine – of which compounded drugs are an essential component.

Bulk Drug Substances Nominated at this Time

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency's criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine

Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium L5 Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutiathone
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene

Pyridoxal 5-Phosphate
Resveratrol
Salicinium
Thymol Iodide

AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA's approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act") – particularly for drugs that have been safely used for years, not only with the Agency's implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals. The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA's complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients' clinical outcomes than provided a bona fide contribution to patient safety.

Conclusion

AANP appreciates the Agency's consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Choline chloride
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)? *Provide an explanation for why it is considered an active ingredient when it is used in specific compounding drug products, and provide citations to specific sources that describe its active properties.*	Yes. There is ample information in PubMed. Please access this article: J Nutr. 2013 Dec 24. [Epub ahead of print] Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL.
Is the ingredient listed in any of the three sections of the Orange Book?	Not for choline chloride
Were any monographs for the ingredient found in the USP or NF monographs?	Not for choline chloride
What is the chemical name of the substance?	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, chloride
What is the common name of the substance?	Choline chloride
Does the substance have a UNII Code?	45I14D8O27
What is the chemical grade of the substance?	USP Dietary monograph for this bulk drug substance available This material is FCC graded
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received Raw material is a generally recognized as safe (GRAS) dietary supplement. and can be supplied by a 510-FDA registered manufacturer
How is the ingredient supplied?	Choline chloride is a white to off white hygroscopic crystal.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 200-655-4). Canada: Listed on Canadian Domestic Substance List (DSL). China: Listed on National Inventory. Japan: Listed on National Inventory (ENCS). Korea: Listed on National Inventory (KECI). Philippines: Listed on National Inventory (PICCS). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	As a single API preparation or in a combination preparation from 25 mg/mL to 100 mg/mL, multiple dose or preservative free, in various sizes up to 30 mL. The proposed product will be compounded as a sterile injectable in various concentrations ranging from 25 mg/mL to 100 mg/mL, 30 mL multiple dose or preservative free vial, and an example formulation is below. Each mL contains: Choline chloride 50 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, in various concentrations and formulations containing Choline chloride and other vitamins, supplements and/or minerals, packaged in various sizes ranging from 10 mL to 30 mL, multiple dose vial, or preservative free vial. Some example formulations are below. Each mL contains: Inositol 50 mg Choline chloride 50 mg L-methionine 25 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous, intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. 2. J Biol Chem. 2013 Jan 11;288(2):837-47. doi: 10.1074/jbc.M112.415117. Epub 2012 Nov 25. Choline supplementation promotes hepatic insulin resistance in phosphatidylethanolamine N-methyltransferase-deficient mice via increased glucagon action. Wu G, Zhang L, Li T, Zuniga A, Lopaschuk GD, Li L, Jacobs RL, Vance DE. 3. Biochim Biophys Acta. 1997 Sep 4;1348(1-2):142-50. Phosphatidylethanolamine N-methyltransferase from liver. Vance DE, Walkey CJ, Cui Z. 4. PLoS One. 2014 Jan 15;9(1):e85848. doi: 10.1371/journal.pone.0085848. eCollection 2014. Lipid Metabolism, Oxidative Stress and Cell Death Are Regulated by PKC Delta in a Dietary Model of Nonalcoholic Steatohepatitis. Greene MW1, Burrington CM2, Lynch DT2, Davenport SK3, Johnson AK2, Horsman MJ2, Chowdhry S4, Zhang J5, Sparks JD6, Tirrell PC4.

Has the bulk drug substance been used previously to compound drug product(s)?	Yes. For many decades.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Supplementation as exogenous source of choline for metabolic pathways.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are no FDA-approved injectable products containing choline chloride as a single API or in a combination.
Is there any other relevant information?	Thousands of patients with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by integrative, alternative and naturopathic physicians daily. Chemically Choline chloride is as stable in aqueous solutions represented by commercial enteral products containing Choline chloride (and other vitamins and minerals) available and stable for at least 12 months. - Ensure® Nutrition Shake - PediaSure® (Retail) Vanilla

ACAM
American College for Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to compound Drug Products in Accordance With Section 503B of Federal Food, Drug, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in instructing physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. We have a strong interest in maintaining the availability of compounded drug products.

We appreciate the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information. In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503B.

ACAM
American College for Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
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F: 406-587-2451
www.acam.org

It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Choline Chloride
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: J Nutr. 2013 Dec 24. [Epub ahead of print] Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL.
What is the chemical name of the substance?	2-Hydroxy-*N,N,N*-trimethylethanaminium chloride
What is the common name of the substance?	Choline
Does the substance have a UNII Code?	45I14D8O27
What is the chemical grade of the substance?	USP Dietary monograph for this bulk drug substance available This material is FCC graded
What is the strength, quality, stability, and purity of the ingredient?	Dietary Supplement grade. A Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Choline chloride, Dietary Supplement is supplied as a white crystalline solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No.200-655-4). Canada: Listed on Canadian Domestic Substance List (DSL). China: Listed on National Inventory. Japan: Listed on National Inventory (ENCS). Korea: Listed on National Inventory (KECI). Philippines: Listed on National Inventory (PICCS). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	There is a USP Dietary Supplement monograph for Choline chloride
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Orally, choline is used for liver disease including chronic hepatitis and cirrhosis, hypercholesterolemia, depression, memory loss, Alzheimer's disease and dementia, and schizophrenia. It is also used orally for body building, delaying fatigue in endurance sports, preventing neural tube defects, preventing cancer, Huntington's chorea, Tourette's disease, cerebellar ataxia, complex partial seizures, asthma, and as a supplement in infant formulas. Intravenously, choline has orphan drug status for TPN-associated hepatic steatosis. (http://naturaldatabase.therapeuticresearch.com/nd/Search.aspx?cs=&s=ND&pt=100&id=436&ds=&name=Choline+Chloride+(CHOLINE)&searchid=48153405)
Are there other drug products approved by FDA to treat the same medical condition?	There are no FDA-approved injectable products containing choline chloride as a single API or in a combination.

If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product? Provide a justification for clinical need, including an estimate of the size of the population that would need the compounded drug.	**Thousands of patients** with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by alternative and naturopathic physicians daily.
Are there safety and efficacy data on compounded drugs using the nominated substance?	272 Covington TR, et al. Handbook of Nonprescription Drugs. 11th ed. Washington, DC: American Pharmaceutical Association, 1996. 1949 Zeisel SH. Choline: needed for normal development of memory. J Am Coll Nutr 2000;19:528S-31S. View abstract. 3094 Yates AA, Schlicker SA, Suitor CW. Dietary reference intakes: The new basis for recommendations for calcium and related nutrients, B vitamins, and choline. J Am Diet Assoc 1998;98:699-706. View abstract. 5139 Gilman AG, et al, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY: Pergamon Press, 1990. 5160 Grunewald KK, Bailey RS. Commercially marketed supplements for bodybuilding athletes. Sports Med 1993;15:90-103. View abstract. 5161 Sehested P, Lund HI, Kristensen O. Oral choline in cerebellar ataxia. Acta Neurol Scand 1980;62:124-6. View abstract. 5162 McNamara JO, Carwile S, Hope V, et al. Effects of oral choline on human complex partial seizures. Neurology 1980;30:1334-6. View abstract. 5163 Shronts EP. Essential nature of choline with implications for total parenteral nutrition. J Am Diet Assoc 1997;97:639-46. View abstract. 5164 Spector SA, Jackman MR, Sabounjian LA, et al. Effect of choline supplementation on fatigue in trained cyclists. Med Sci Sports Exerc 1995;27:668-73. View abstract. 5165 Gupta SK, Gaur SN. A placebo controlled trial of two dosages of LPC antagonist-choline in the management of bronchial
If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	There are no FDA-approved injectable products containing choline chloride as a single API or in a combination, in the concentration prescribed.
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	As a single API preparation or in a combination preparation from 25 mg/mL to 100 mg/mL, multiple dose or preservative free, in various sizes up to 30 mL. The proposed product will be compounded as a sterile injectable in various concentrations ranging from 25 mg/mL to 100 mg/mL, in various sizes up to 30 mL multiple dose or preservative free vial, and an example formulation is below. Each mL contains: Choline chloride 50 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, in various concentrations and formulations containing Choline chloride and other vitamins, supplements and/or minerals, packaged in various sizes ranging from 10 mL to 30 mL, multiple dose vial, or preservative free vial. Some example formulations are below. Each mL contains: Inositol 50 mg Choline chloride 50 mg L-methionine 25 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Intravenous, intramuscular
Has the bulk drug substance been used previously to compound drug product(s)?	Yes. Please see above.
Is there any other relevant information?	Chemically speaking Choline chloride should be as stable in aqueous solutions since there are commercial enteral products containing Choline chloride (and other vitamins and minerals) available and stable for at least 12 months. - Ensure® Nutrition Shake - PediaSure® (Retail) Vanilla - Boost® Original

VIA WWW.REGULATIONS.COM

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations.

To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration's request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food Drug and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the

process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

American Academy of Environmental Medicine (AAEM) www.aaemonline.org
American Association of Naturopathic Physicians (AANP) www.naturopathic.org
American College for Advancement in Medicine (ACAM) www.acam.org
International College of Integrative Medicine (ICIM) www.icimed.com
International Hyperbaric Medical Association (IHMA) www.hyperbaricmedicalassociation.org
International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and subject to Category

I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

IMC Objections and Requests Regarding Docket FDA-2013-N-1525

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA's approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act"), particularly for drugs that have been in use for years, not only with FDA's at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions.

This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the

track record in this industry. This is particularly true given that the infectious contamination that gave rise to the Act has little to do with the approval process for which ingredients may be compounded. Yet FDA has offered little consideration of the respective risks and benefits of its approach, and with pharmacies and physicians carrying the full burden of proof and the time expected for the advisory process to conclude, the FDA will likely itself cause more patient harm than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for "Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness," 79 FR 37687, in which 25 drugs were added to the list of barred drugs, it has not done so for the much broader issue of upending the compounding pharmaceutical industry, which bears costs both in preparation of detailed submissions on potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic consequence to physicians of not being to prescribe these drugs, and the economic impacts of health difficulties and added expense that will result from the withdrawal of drugs from clinical use. The Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC's March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug substances. IMC identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring.[1] We had determined that at least 6 hours per ingredient would be needed to do so, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

[1] For example, other nominations would include 7 Keto Dehydroepiandrosterone; Asparagine; Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin; Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid; Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol Iodide.

day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.

This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use,[2] and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

[2] Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Choline chloride
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)? *Provide an explanation for why it is considered an active ingredient when it is used in specific compounding drug products, and provide citations to specific sources that describe its active properties.*	Yes. There is ample information in PubMed. Please access this article: J Nutr. 2013 Dec 24. [Epub ahead of print] Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL.
Is the ingredient listed in any of the three sections of the Orange Book?	Not for choline chloride
Were any monographs for the ingredient found in the USP or NF monographs?	Not for choline chloride
What is the chemical name of the substance?	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, chloride
What is the common name of the substance?	Choline chloride
Does the substance have a UNII Code?	45I14D8O27
What is the chemical grade of the substance?	USP Dietary monograph for this bulk drug substance available This material is FCC graded
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received Raw material is a generally recognized as safe (GRAS) dietary supplement. and can be supplied by a 510-FDA registered manufacturer
How is the ingredient supplied?	Choline chloride is a white to off white hygroscopic crystal.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 200-655-4). Canada: Listed on Canadian Domestic Substance List (DSL). China: Listed on National Inventory. Japan: Listed on National Inventory (ENCS). Korea: Listed on National Inventory (KECI). Philippines: Listed on National Inventory (PICCS). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	As a single API preparation or in a combination preparation from 25 mg/mL to 100 mg/mL, multiple dose or preservative free, in various sizes up to 30 mL. The proposed product will be compounded as a sterile injectable in various concentrations ranging from 25 mg/mL to 100 mg/mL, 30 mL multiple dose or preservative free vial, and an example formulation is below. Each mL contains: Choline chloride 50 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, in various concentrations and formulations containing Choline chloride and other vitamins, supplements and/or minerals, packaged in various sizes ranging from 10 mL to 30 mL, multiple dose vial, or preservative free vial. Some example formulations are below. Each mL contains: Inositol 50 mg Choline chloride 50 mg L-methionine 25 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous, intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. 2. J Biol Chem. 2013 Jan 11;288(2):837-47. doi: 10.1074/jbc.M112.415117. Epub 2012 Nov 25. Choline supplementation promotes hepatic insulin resistance in phosphatidylethanolamine N-methyltransferase-deficient mice via increased glucagon action. Wu G, Zhang L, Li T, Zuniga A, Lopaschuk GD, Li L, Jacobs RL, Vance DE. 3. Biochim Biophys Acta. 1997 Sep 4;1348(1-2):142-50. Phosphatidylethanolamine N-methyltransferase from liver. Vance DE, Walkey CJ, Cui Z. 4. PLoS One. 2014 Jan 15;9(1):e85848. doi: 10.1371/journal.pone.0085848. eCollection 2014. Lipid Metabolism, Oxidative Stress and Cell Death Are Regulated by PKC Delta in a Dietary Model of Nonalcoholic Steatohepatitis. Greene MW1, Burrington CM2, Lynch DT2, Davenport SK3, Johnson AK2, Horsman MJ2, Chowdhry S4, Zhang J5, Sparks JD6, Tirrell PC4. 5. Breast Cancer Res. 2014 Jan 21;16(1):R5. [Epub ahead of print] Interplay of choline metabolites and genes in patient-derived breast cancer xenografts.

Has the bulk drug substance been used previously to compound drug product(s)?	Yes. For many decades.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Supplementation as exogenous source of choline for metabolic pathways.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are no FDA-approved injectable products containing choline chloride as a single API or in a combination.
Is there any other relevant information?	Thousands of patients with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by integrative, alternative and naturopathic physicians daily. Chemically Choline chloride is as stable in aqueous solutions represented by commercial enteral products containing Choline chloride (and other vitamins and minerals) available and stable for at least 12 months. - Ensure® Nutrition Shake - PediaSure® (Retail) Vanilla - Boost® Original

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee ***prior*** to the implementation and issuance of regulations including the creation of the bulk ingredient list.

> (2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

> General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Choline Chloride
Chemical/Common Name	(2-Hydroxyethyl)trimethylammonium Chloride
Identifying Codes	67-48-1
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies *(including foreign recognition)*	USP Food Codex Compendium

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography *(where available)*	
Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension

The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a "deficiency letter" be issued to the person or organization that submitted the nomination? The Agency issues "deficiency letters" for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue "deficiency letters" to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Choline chloride
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)? *Provide an explanation for why it is considered an active ingredient when it is used in specific compounding drug products, and provide citations to specific sources that describe its active properties.*	Yes. There is ample information in PubMed. Please access this article: J Nutr. 2013 Dec 24. [Epub ahead of print] Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL.
Is the ingredient listed in any of the three sections of the Orange Book?	Not for choline chloride
Were any monographs for the ingredient found in the USP or NF monographs?	Not for choline chloride
What is the chemical name of the substance?	Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, chloride
What is the common name of the substance?	Choline chloride
Does the substance have a UNII Code?	45I14D8O27
What is the chemical grade of the substance?	USP Dietary monograph for this bulk drug substance available This material is FCC graded
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received Raw material is a generally recognized as safe (GRAS) dietary supplement. and can be supplied by a 510-FDA registered manufacturer
How is the ingredient supplied?	Choline chloride is a white to off white hygroscopic crystal.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances (EINECS No. 200-655-4). Canada: Listed on Canadian Domestic Substance List (DSL). China: Listed on National Inventory. Japan: Listed on National Inventory (ENCS). Korea: Listed on National Inventory (KECI). Philippines: Listed on National Inventory (PICCS). Australia: Listed on AICS.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection

What strength(s) will be compounded from the nominated substance?	As a single API preparation or in a combination preparation from 25 mg/mL to 100 mg/mL, multiple dose or preservative free, in various sizes up to 30 mL. The proposed product will be compounded as a sterile injectable in various concentrations ranging from 25 mg/mL to 100 mg/mL, 30 mL multiple dose or preservative free vial, and an example formulation is below. Each mL contains: Choline chloride 50 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, in various concentrations and formulations containing Choline chloride and other vitamins, supplements and/or minerals, packaged in various sizes ranging from 10 mL to 30 mL, multiple dose vial, or preservative free vial. Some example formulations are below. Each mL contains: Inositol 50 mg Choline chloride 50 mg L-methionine 25 mg 1 % Benzyl alcohol as a preservative in Water for Injection q.s. Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous, intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High-Fat Diet. Al Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. 2. J Biol Chem. 2013 Jan 11;288(2):837-47. doi: 10.1074/jbc.M112.415117. Epub 2012 Nov 25. Choline supplementation promotes hepatic insulin resistance in phosphatidylethanolamine N-methyltransferase-deficient mice via increased glucagon action. Wu G, Zhang L, Li T, Zuniga A, Lopaschuk GD, Li L, Jacobs RL, Vance DE. 3. Biochim Biophys Acta. 1997 Sep 4;1348(1-2):142-50. Phosphatidylethanolamine N-methyltransferase from liver. Vance DE, Walkey CJ, Cui Z. 4. PLoS One. 2014 Jan 15;9(1):e85848. doi: 10.1371/journal.pone.0085848. eCollection 2014. Lipid Metabolism, Oxidative Stress and Cell Death Are Regulated by PKC Delta in a Dietary Model of Nonalcoholic Steatohepatitis. Greene MW1, Burrington CM2, Lynch DT2, Davenport SK3, Johnson AK2, Horsman MJ2, Chowdhry S4, Zhang J5, Sparks JD6, Tirrell PC4. 5. Breast Cancer Res. 2014 Jan 21;16(1):R5. [Epub ahead of print] Interplay of choline metabolites and genes in patient-derived breast cancer xenografts.

Has the bulk drug substance been used previously to compound drug product(s)?	Yes. For many decades.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Supplementation as exogenous source of choline for metabolic pathways.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There ar no FDA-approved injectable products containing choline chloride as a single API or in a combination.
Is there any other relevant information?	Thousands of patients with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by alternative and naturopathic daily. Chemically speaking Choline chloride should be as stable in aqueous solutions since there are commercial enteral products containing Choline chloride (and other vitamins and minerals) available and stable for at least 12 months. - Ensure® Nutrition Shake - PediaSure® (Retail) Vanilla - Boost® Original

Tab 3b

Choline Chloride
Nomination Clarification

Alliance for Natural Health USA
3525 Piedmont Road NE
Building 6, Suite 310
Atlanta, GA 30305

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
anhinternational.org

January 26, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Avenue
Building 51, Room 3249
Silver Spring, MD 20903

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman:

The Alliance for Natural Health USA (ANH-USA) is responding to FDA's questions regarding the nomination of **Choline Chloride** for inclusion on the 503A bulk drug substances list.

ANH-USA is an independent, nonprofit watchdog organization of more than 550,000 members nationally that protects consumer access to natural health services, practitioners, and resources. Safely compounded medications, as provided by integrative physicians, fulfill an important clinical need for many of our members. These are patients who have not found relief for their health conditions through conventional means. Such patients often have an adverse reaction to mass-manufactured drugs, and require a more individualized treatment regimen.

Before providing our responses, we wish to object to what has apparently evolved into a new request for a disease indication rather than simply a use for the ingredient. The implication is that FDA approval will be based upon a disease indication when functional and nutraceutical uses have substantial clinical value and are plainly lawful under the Food, Drug, and Cosmetic Act.

Responses:

Q1. Does Alliance for Natural Health USA still want to pursue review by the FDA and consideration by the PCAC of choline chloride for inclusion on the 503A bulks list?

A. Yes

Q2. Your nomination proposes choline chloride for "supplementation as [an] exogenous source of choline for metabolic pathways," which is not a disease state or health condition. Please submit in

writing the disease state(s) or health condition(s) that you are proposing for FDA's review, the dosage form and strength/concentration proposed for each use, and scientific articles in support of each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. ANH-USA cites the response of McGuff Compounding Pharmacy Services and the American Association of Naturopathic Physicians, both of which possess the necessary expertise on this matter.

ANH-USA appreciates the FDA's and its Pharmacy Compounding Advisory Committee's (PCAC) consideration of this further information in support of the nomination of Choline Chloride for inclusion on the 503A bulk drug substances list. We would like to reiterate that the Agency's original request asked only for ingredients' proposed use, not the disease condition or indication.

If you have further questions, please contact me.

Sincerely,

Michael Jawer
Deputy Director

Email: mike@anh-usa.org
Phone: 240-396-2171

VIA EMAIL
toni.hallman@fda.hhs.gov

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
Food and Drug Administration
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

Re: Response to Requests for More Information on Nominations for Alpha Lipoic Acid, Methyl B12 and Choline Chloride
Docket FDA-2015-N-3534

Dear LT. Hallman:

I write on behalf of the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the three above-named ingredients. It is correct that IMC and AANP maintain these nominations as ingredients that should be placed on the 503A positive list. In addition to providing what material we can in the short time provided, I write to object to the unreasonably short time allowed and request and extension to file a more complete response. Of more import, we also object to what has evolved into a new request for a disease indication rather than simply a use for an ingredient, and its implication that approval must be based upon a disease indication when functional uses have great clinical utility and are plainly lawful under the language of the Food, Drug and Cosmetic Act ("FDCA").

Enclosed please find three submissions addressing the questions raised for response by today, though we intend to supplement these filings. We also are in support of submissions made by co-nominators the Pharmacy Compounding Centers of America and McGuff Compounding Pharmacy.

Objection As to Insufficient Notice

IMC and AANP appreciate that FDA is seeking additional information as it weighs our nominations, but the due date of January 26, 2018 for much of the information was only submitted to our organizations on January 16th. A ten-day window, particularly for physicians and pharmacists engaged in full-time practices, is not reasonable. We appreciate that staff would

like time to review clinical materials prior to the as yet unannounced PCAC meeting, but the requests are quite extensive. We are therefore providing what we can in the limited time allowed but request until February 23, 2018 to supplement our responses along with the other questions requested by that date.

The request regarding alpha lipoic acid, for example, asks for at least one study for the 23 proposed indications that were submitted for that ingredient. Submissions by AANP, IMC and co-nominators McGuff Compounding Pharmacy and the Professional Compounding Centers of American have previously provided citations to over 280 articles, the indication for most which can plainly be seen in the titles as referring to diabetic neuropathy or other conditions. The statement that indications will not be reviewed unless we submit additional materials, and in a ten-day window, given the extent of the materials already provided, is concerning. Given, as well, the FDA's evident policy on ingredients under review that a single study is insufficient to gain approval, the actual burden for all three ingredients made in these requests is much higher.

Further, the request to break down the dosage and form by each proposed use is not contained in the Federal Register Notice (2015-27271) but constitutes a new request, as is the request to provide supportive statements from the materials of professional medical societies and to prioritize all uses. Further, while we appreciate that the FDA is following up on our previous submissions, the original request only asks for the "proposed use" and does not ask for the disease indication or condition. These are all significant requests that cannot be reasonably accomplished in ten days.

Objection as to Requirements of a Disease Indication

IMC and AANP object to the requirement that an ingredient demonstrate that it has an indication for a disease or condition to sustain a nomination. Such a requirement is neither clinically required nor lawful as certain ingredients are used solely for their functional effects or nutraceutical value and may not be intended to treat, cure or even prevent specific disease states. While our nominations state and we believe evidence and experience show that these ingredients indeed have a role to play in preventing, mitigating or treating disease, the presumption that an item may be refused placement on the positive list even if there may be proper and legitimate functional or nutritional uses as their sole basis is not clinically or legally grounded.

While we understand that FDA is focused on the disease model and this language might at first reading have unintentionally excluded functional uses of ingredients, FDA's briefing documents have thus far excluded consideration of functional uses. Further, the request for information for choline chloride specifically asks, for example, for the "disease state(s) or health condition(s)" we are proposing, and states that "neuropathic disorder" is insufficiently precise, suggesting not only that a disease state is required but that it must even be presented with ICD-10 or similar

specificity. A claim of treating "neuropathic disorders" would certainly qualify as an improper drug claim on an unapproved product, and basing approval upon whether a physician chooses to use choline chloride for peripheral, autonomic, diabetic or other form of neuropathy within the scope of their training seeks to apply an improperly high threshold to matters that fall within the purview of state overseen medical and compounding practice. While we appreciate the effort to focus the review of the clinical evidence, to the extent that a disease indication were the basis for use, as long as choline chloride, in this example, is shown to have a valid role in any form of neuropathy that should be sufficient to allow a physician to the ability access for their patients as guided by his or her knowledge and experience. While I won't burden this letter with the extensive citations available on the topic, the FDA's regulatory authority and jurisdiction is limited by the right of physicians to practice medicine. Compounding pharmacies are not permitted to market their ingredients with therapeutic claims in any event. Finally, the request for specificity seems plainly contrary to the lack of FDA authority to limit the use of a compounded ingredient placed on the positive list to certain indications.

The Legal Requirement for Ingredient "Use"

Imposing a disease model on compounding practice is expressly contrary to the FDCA, which defines a drug as including products that affect the function of the body. 21 U.S.C. § 321(g)(C). Nothing in that definition limits either the definition or proper use of a drug to the disease claim listed separately at 21 U.S.C. § 321(g)(B).[1] If one markets an ingredient with the sole claim that it affects physiologic function without first obtaining NDA approval, the FDA can and routinely does issue warning letters or take enforcement actions to remove such products from the market. The converse is also true; where a product provides functional support it is properly a drug that should be considered on the merits of that claim without imposing a requirement that there be a disease indication. Whether an oversight or intentional effort to remove an entire basis for use, the FDA cannot have it both ways in its interpretation of its enabling legislation.

Where a pharmacist compounds on lawful scripts for the prescriber's purpose of affecting physiologic function, such as to provide a high level of antioxidant or anti-inflammatory activity, and no claim made about disease treatment, the FDA's criteria imposes a burden of proof for a claim that was not undertaken by the pharmacist or physician and improperly restricts an entire basis for clinically proper and lawful use. Further, assessing claims has always been based upon manufacturer's intent, which is not applicable to physician prescribing.

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[1] "The term "drug" means . . (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals..." 21 U..C. § 321(g).

Nothing in the language of the Drug Quality and Security Act ("DQSA") (P.L. 113-54) or the Food and Drug Administration Modernization and Accountability Act of 1997 (P.L. 105-115) ("FDAMA") limits this definition of a "drug" nor provides any basis for restricting compounded drugs to disease indications.

Functional Uses

Support for optimal function or therapeutic support are legitimate purposes undertaken by medical and naturopathic care that are completely missing from FDA consideration. Clinical modeling and evidence of the role of antioxidants, for example, in optimal functioning are less susceptible to controlled study but the evidence for many of these ingredients for such use is nonetheless ample. Alpha lipoic acid is a potent anti-oxidant, which is a valuable support for healthy functioning. The health effects of antioxidants are well-recognized, and as an ingredient in a compounded formulation could have obvious value. Ingredients that have recognized anti-inflammatory effects[2] have been recommended for denial by FDA because of its position that physicians should not be able to offer such support to their patients unless the evidence reaches the additional threshold of evidence that it can treat a disease. The FDA did not make that part of its request of nominators in its original request, nor has not subjected the wisdom of this health policy to notice and comment, as it is but one of many major health policy decisions that are completely absent[3] from its December 16, 2015 Anticipated Notice of Proposed Rulemaking "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," failing both in its legal duties and obligations to understand the arena it is regulating.

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[2] The FDA recommended the denial of resveratrol, for example, which it considered for both for the treatment of pain and impaired glucose tolerance. In its briefing paper the FDA noted that "Resveratrol appears to have anti-inflammatory, antioxidant, anticancer, and other effects in many in vitro, ex vivo and in vivo models." November 20, 2017 PCAC meeting, Briefing Paper on Resveratrol at 29. While the FDA was concerned about bioavailability and bimodal dosing responses, this was within the context of managing disease and not an assessment of the role it can play as an antioxidant in prevention and functional support for wellness. Other examples of the complete disregard for functional purposes thus far include N-acetyl-D-glucosamine, 5-HTP (oxitriptan), alanyl-L-glutamine, acetyl-L-carnitine, and N-acetyl-D-glucosamine (recommended for disapproval for oral use).

[3] *See* nominators comments on "Proposed Rule: List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," Docket No. FDA-2016-N-3464 dated March 16, 2018.

This omission of functional care considerations has been pervasive in the ingredient review process as many of the ingredients reviewed have been ingredients marketed as dietary supplements for functional purposes. Physician prescribed combinations of nutrients may be used by physicians practicing functional medicine pursuant to schools of medical or naturopathic thought, taught in properly recognized universities or credentialed educational programs that receive ACCME Category I CME certification. This field of practice has been unrecognized and entirely overlooked in FDA's regulatory scheme; it has taken no evidence, consulted no experts in the field of nutritional, functional or naturopathic medicine, and made no findings. Our submissions of these three products provide examples of such uses and FDA should not impose a disease claim requirement where actual practice is not based on such claims. The rejection without comment of a field of recognized care is arbitrary and capricious as a legal matter and poor practice as a matter or public health policy.

Nutritional Uses

Some compounded products may also provide convenient, tailored nutrient support specific to the health needs of a patient. This promotes convenient use, avoids allergens and contaminants, and in some cases may include prescription items as part of an overall treatment and support approach. Patients may require compounded ingredients due to difficulties consuming whole foods or specific kinds of foods or benefit from dietary supplementation which provides nutrients otherwise not readily available due to special or limited diets. Creating mixtures of formulated nutraceuticals can increase patient compliance, maximize synergistic effects and assist in treating difficulties with absorption or other digestive issues. Sublingual routes of administration may also be of help with ingredients which present absorption issues in certain patients.

This is a form of compounding practice about which the FDA has taken no cognizance and thus has not addressed its value.

The Role of the United States Pharmacopeia Dietary Ingredient Monographs

The rejection of the United States Pharmacopeia ("USP") dietary ingredient monographs generally, and of specific nutraceuticals as the process moves forward, threatens to eliminate these entire methods of practice. Whether or not this is by design, the FDA has shown no signs that it is aware of this practice or the impact it's regulatory course is having upon it. There has been no discussion in the Compliance Policy Guidance documents, federal register, PCAC briefing documents or in the PCAC meetings about this practice. No voting member of the PCAC Committee has any training or experience in this form of practice. Compounding pharmacists have always been free to compound items listed in the USP and for the purposes described in this letter are an important practice that should continue.

However these issues are ultimately addressed, the FDA's requirement for a disease indication and restrictive reviews of ingredients based on a concern that physicians may use a dietary supplement for functional or therapeutic purposes ignores areas of medical and naturopathic practice outside of FDA's expertise. Physicians with training and experience in such use, whether because of anticipated therapeutic effects or unique assimilation issues should be legally allowable without each nutrient having to go through disease indication levels of scrutiny.

We would appreciate it if you would share this letter with the members of the PCAC so that our concerns may be considered directly by the Committee.

Sincerely,

Alan Dumoff

Enclosures
AANP / IMC submission for alpha-lipoic acid
AANP / IMC submission for choline chloride
AANP / IMC submission for methylcobalamin

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Alpha Lipoic Acid
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organization still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulk list?

A. Yes.

Q. Please explain whether the nominated molecule is enantiomerically pure or a racemic mixture.

A. Racemic mixture.

Q. Alpha lipoic acid is minimally soluble in water and unstable unless protected from air and light. Please provide any information available about how these issues are addressed for compounded products, especially intravenous formulations.

A. Co-nominator McGuff Compounding Pharmacy has performed a stability study on for its alpha lipoic acid compounded preparations to demonstrate formulation stability through the assigned Beyond-Use Date.

The following parameters were examined and/or tested as part of the stability program:

i. Appearance, seal
ii. Appearance, vial
iii. Appearance, preparation
iv. Foreign matter, visible particulate
v. pH
vi. Potency assay, HDLC
vii. Sterility
viii. Antitoxin
ix. Method suitability, sterility test
x. Container closure integrity
xi. Preservative effectiveness (for multi-dose vial)
xii. Preservative concentration (for multi-dose vial)

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific

article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration and compounded dosage form is a oral capsules ranging from 100 to 500 mg, topical use and parenteral injection of 25 mg/mL or 40 mg/mL concentration. The listing below includes some of the known uses for alpha lipoic acid:

Diabetic neuropathic pain [For e.g., ICD-10 E13.40; Ideopathyic Neuropathy ICD-10G60.9]. ALA is an approved treatment for diabetic neuropathy in Germany.

a. "Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy." Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Möller W, Tritschler HJ, Mehnert H. Free Radic Res 1999 Sep; 31(3): 171-9.

b. "Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy." Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R. Diabetes Care. 1999 Aug;22(8):1296-301.

c. "Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?" A Review by Mijnhout, A. Alkhalaf, N. Kleefstra, HJG. Neth J Med 2010 Apr; 68(4):158-62.

d. "Preventing complications and treating symptoms of diabetic peripheral neuropathy." Comparative Effectiveness Review Number 187. Johns Hopkins University Evidence-based Practice Center.

e. "Predictors of improvement and progression of diabetic polyneuropathy following treatment with a-lipoic acid for 4 years in the NATHAN 1 trial." Ziegler D, Low PA, Freeman R, Tritschler H, Vinik AI. J Diabetes Complications. 2016 Mar;30(2):350-6.

Pancreatic cancer [For e.g., ICD-10 D01.7]

a. "The long-term survival of a patient with stage iv renal cell carcinoma following an integrative treatment approach including the intravenous alpha-lipoic acid/low-dose naltrexone protocol." Berkson, BM and Calvo, RF. Integr Cancer Ther 2017 Dec 1 epub.

b. "Revisiting the ALA/N (a-lipoic acid/low-dose naltrexone) protocol for people

with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases." Berkson BM, Rubin DM, Berkson AJ. Integr Cancer Ther 2009 8: 416.

Hepatitis C [For e.g., ICD-10 B17.10]

a. "A conservative triple antioxidant approach to the treatment of hepatitis c combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories." Berkson BM. MEd Klin (Munich) 1999: Oct 15;94 Suppl 3:84-9.

Liver Disease, Cirrhosis and Toxic Disease [For e.g., ICD-10 K71.8]

a. "Alpha lipoic acid and liver disease." Berkson, BM. Townsend Letter, Dec 2007.

b. "Lipoic acid in liver metabolism and disease" Bustamente, J. Lodge, JK, Marcocci L, Tritschler HJ, Packer L, Rihn BH. Free Radic Biol Med. 1998 Apr; 24(6):1023-39.

Mushroom Poisoning [For e.g., ICD-10 T62.0X1A]

a. "Thioctic acid in the treatment of poisoning with alpha-amanita." Barter and Berkson.

Fibromyalgia and Muscle Pain [For e.g., M78.7]

a. "Innovations in the management of musculoskeletal pain with alpha-lipoic acid (impala trial): study protocol for a double-blind, randomized, placebo-controlled crossover trial of alpha-lipoic acid for the treatment of fibromyalgia pain." Gilron L, Tu D, Holden R, Towheed T, Ziegler D, Wang L, Milev R, Gray C. AMIR Res Protoc 2017 Mar 28;6(3).

Q. Prioritize the uses of alpha lipoic acid in order of strongest to weakest scientific support.

A. The following conditions are prioritized for the uses of alpha lipoic acid from strongest to weakest scientific support: diabetic neuropathy, hepatitis, fibromyalgia and pancreatic cancer.

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Methylcobalamin
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Methylcobalamin inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of Methylcobalamin for inclusion on the 503A bulk list?

A. Yes.

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide scientific articles supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration include oral, ranging from 500 to 5000 mcg; sublingual, ranging from 500 mcg to 5000 mcg troche or liquid; nasal, ranging from 250-500 mcg/spray 0.1 ml; and parenteral subcutaneous injection or infusions ranging from 0.5 mg/mL to 12.5 mg/mL for all listed uses for methylcobalamin below:

Autistic Spectrum Disorder [For e.g., ICD-10 F84.0]

a. "Treatments for biomedical abnormalities associated with autism spectrum disorder." Frye RE, Front Pediatr 2014 June 27;2:66.

b. "Randomized, placebo-controlled trial of methyl b12 for children with autism." Hendren RL." James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. J Child Adolesc Psychopharmacol. 2016 Nov, 26(9):774-783.

c. "Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism." James SJ, Melnyk S, Fuchs G, et al. Am J Clin Nutr. 2009;89(1):425-30.

d. "Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism." James SJ, Cutler P, Melnyk S, et al. Am J Clin Nutr. 2004 Dec;80(6):1611-7.

e. "Effectiveness of methylcobalamin and folinic acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status." Frye, RE, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters, L, James SJ. Autism Res Treat. 2013 Oct 12:epub.

Diabetic and Idiopathic Neuropathy [For e.g., ICD-10 E13.40; Idiopathic Neuropathy G60.9; Neualgia and neuritis M79.2]

a "Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials." Sun Y. Acta Neurol Taiwan. 2005; June 14(2): 48-54.

b. "Intravenous methylcobalamin treatment for uremic diabetic neuropathy in chronic hemodialysis patients." S. Kuwabara. Intern Med. 1999. Jun; 38(6):472-5.

Pain Management [For e.g. ICD-10 G89.4]

a. "Intravenous and intrathecal methylcobalamin: a potential vitamin of pain killer." Zhang. Neuro Plast 2013 Epub 2013 Dec 26.

Amyotrophic Lateral Sclerosis [For e.g., ICD-10 G12.21]

a. "Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study." Kaji R, Kodama M, Imamura A, et al. Muscle Nerve. 1998;21(12):1775-8.

b. "Neuroprotective effect of ultra-high dose methylcobalamin in wobbler mouse model of amyotrophic lateral sclerosis." Ikeda K, Iwasaki Y, Kaji R. J Neuro Sci. 2015 Jul 15;354(1-2:70-4.

Genetic Metabolic Disorders, such as MTHFR [For e.g., ICD-10 Z15.89]

a. "Anxiety and Methylenetetrahydrofolate Reductase Mutation Treated With S-Adenosyl Methionine and Methylated B Vitamins." Anderson S, Panka J, Rakobitsch R, Tyre K, Pulliam K. Integrative Medicine: A Clinician's Journal. 2016;15(2):48-52.

Q. Provide additional information you believe would be useful for us to consider.

A. There is an FDA registered medical food, METANX, with Methyl B-12 as a primary ingredient. The claim is for usefulness in multiple disorders and lists numerous references. *See* http://www.metanx.com/pdf/METANXCapsulesPIStatement.pdf
It has safety data and has been in use over 5 years. It has common allergens [MILK AND SOY] which provides an additional reason that it should be available to compound PO.

STATED INDICATIONS: METANX® is indicated for the distinct nutritional requirements of individuals with endothelial dysfunction who present with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy. METANX® is also indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia who present with lower extremity ulceration(s).

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Choline Chloride
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of choline for inclusion on the 503A bulk list?

A. Yes.

Q. Please submit in writing the disease state(s) or health condition(s) that you are proposing for the FDA's review, the dosage form and strength/concentration proposed for each use, and scientific articles in support of each use.

A, Without waiving the objections contained in the accompanying letter, at the compounded dosage and delivery of a parenteral injection of 50 mg/mL concentration as a chloride salt, the listing below includes some of the known uses for choline:

Liver Diseases; Hepatic Steatosis [For e.g., ICD-10 K70.0, K76.0]

a. "Studies on the Effects of Intravenously Administered Choline Chloride in Patients with and without Liver Disease." Stegmann. J. 1953.

b. "Choline supplementation protects against liver damage by normalizing cholesterol metabolism in Pemt/Ldlr knockout mice fed a high-fat diet." Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. J Nutr. 2014 Mar;144(3):252-7.

c. "The Addition of Choline to Parenteral Nutrition." Buchman A. Gastroenterology 2009 Nov;137 (5 Suppl):S119-128 (Steatosis).

d. "Revisiting the ALA/N (a-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases." Berkson BM, Rubin DM and Berkson AJ. Integr Cancer Ther 2009 8: 416.

Fetal Alcohol Spectrum Disorder

a. "Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders." Nguyen TT Risbud RD, Mattson SN, Chambers CD, Thomas JD. Am J Clin Nutr. 2016 Dec;104(6):1683-1692. Epub 2016 Nov 2.

Atherosclerosis

a. Lipotropic factors and atherosclerosis; action of methionine, choline and inositol on experimental cholesterol atherosclerosis. Capretti G, Paglia G. G Clin Med. 1950 Sep;31(9):1120-37.

b. ["Action of lipotropic factors in atherosclerosis"]. Concours Med. 1954 Nov 13;76(46):4207-9. [Article in French] Millot J (French)

Functional Support [For e.g., ICD-10 G31.84]

a. "Citicoline improves memory performance in elderly subjects." Alvarez XA, Laredo M, Corzo D, Fernández-Novoa L, Mouzo R, Perea JE, Daniele D, Cacabelos R Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):201-10.

Jan. 26, 2018

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903
Email: toni.hallman@fda.hhs.gov

RE: Docket FDA-2015-N-3534, Choline

Dear Ms. Hallman,

McGuff Compounding Pharmacy Services, Inc. (MCPS) is responding to the FDA's questions to the nomination of Choline inclusion on the 503A bulk drug substances list due by Jan. 26, 2018.

Responses:

Q. Does MCPS still want to pursue review by the FDA and consideration by the PCAC of choline for inclusion on the 503A bulk list?

A. Yes.

Q. Please submit in writing the disease state(s) or health condition(s) that you are proposing for the FDA's review, the dosage form and strength/concentration proposed for each use, and scientific articles in support of each use.

A. The compounded dosage form is a parenteral injection of 50 mg/mL concentration as a chloride salt. The listing below includes some of the known uses for choline:

Liver Diseases

a. "Studies on the Effects of Intravenously Administered Choline Chloride in Patients with and without Liver Disease." F. Stegmann 1953.

Hepatic Steatosis

b. "The Addition of Choline to Parenteral Nutrition." A. Buchman 2009.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

Non-alcoholic Fatty Liver Disease

c. "Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in Pemt/Ldlr Knockout Mice Fed a High Fat Diet." Ala Al Rajabi 2014.

Fetal Alcohol Spectrum Disorder

d. "Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial." J Wozniak.

Please let us know if you are in need of any further information.

Sincerely,

Ronald M. McGuff, President/CEO
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., STE 142
Santa Ana, CA 92704

The Journal of Nutrition
Biochemical, Molecular, and Genetic Mechanisms

Choline Supplementation Protects against Liver Damage by Normalizing Cholesterol Metabolism in *Pemt/Ldlr* Knockout Mice Fed a High-Fat Diet[1,2]

Ala Al Rajabi,[3] Gabriela S. F. Castro,[5] Robin P. da Silva,[3] Randy C. Nelson,[3] Aducio Thiesen,[4] Helio Vannucchi,[5] Donna F. Vine,[3] Spencer D. Proctor,[3] Catherine J. Field,[3] Jonathan M. Curtis,[3] and René L. Jacobs[3]*

Departments of [3]Agricultural, Food, and Nutritional Science, and [4]Lab Medicine and Pathology, University of Alberta, Edmonton, AB, Canada; and [5]Department of Internal Medicine, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Abstract

Dietary choline is required for proper structure and dynamics of cell membranes, lipoprotein synthesis, and methyl-group metabolism. In mammals, choline is synthesized via phosphatidylethanolamine *N*-methyltransferase (*Pemt*), which converts phosphatidylethanolamine to phosphatidylcholine. *Pemt*$^{-/-}$ mice have impaired VLDL secretion and developed fatty liver when fed a high-fat (HF) diet. Because of the reduction in plasma lipids, *Pemt*$^{-/-}$/low-density lipoprotein receptor knockout (*Ldlr*$^{-/-}$) mice are protected from atherosclerosis. The goal of this study was to investigate the importance of dietary choline in the metabolic phenotype of *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ male mice. At 10–12 wk of age, *Pemt*$^{+/+}$/*Ldlr*$^{-/-}$ (HF$^{+/+}$) and half of the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ (HF$^{-/-}$) mice were fed an HF diet with normal (1.3 g/kg) choline. The remaining *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice were fed an HF diet supplemented (5 g/kg) with choline (HFCS$^{-/-}$ mice). The HF diet contained 60% of calories from fat and 1% cholesterol, and the mice were fed for 16 d. HF$^{-/-}$ mice lost weight and developed hepatomegaly, steatohepatitis, and liver damage. Hepatic concentrations of free cholesterol, cholesterol-esters, and triglyceride (TG) were elevated by 30%, 1.1-fold and 3.1-fold, respectively, in HF$^{-/-}$ compared with HF$^{+/+}$ mice. Choline supplementation normalized hepatic cholesterol, but not TG, and dramatically improved liver function. The expression of genes involved in cholesterol transport and esterification increased by 50% to 5.6-fold in HF$^{-/-}$ mice when compared with HF$^{+/+}$ mice. Markers of macrophages, oxidative stress, and fibrosis were elevated in the HF$^{-/-}$ mice. Choline supplementation normalized the expression of these genes. In conclusion, HF$^{-/-}$ mice develop liver failure associated with altered cholesterol metabolism when fed an HF/normal choline diet. Choline supplementation normalized cholesterol metabolism, which was sufficient to prevent nonalcoholic steatohepatitis development and improve liver function. Our data suggest that choline can promote liver health by maintaining cholesterol homeostasis. J. Nutr. 144: 252–257, 2014.

Introduction

Nonalcoholic fatty liver disease (NAFLD)[6] is a term that describes a wide spectrum of hepatic disorders that feature fat accumulation in the liver unrelated to alcohol consumption. The spectrum of NAFLD ranges from simple steatosis (TG accumulation in hepatocytes) to nonalcoholic steatohepatitis [NASH (steatosis with inflammation and fibrosis)], cirrhosis (replacement of hepatocytes by scar tissue), and eventually liver failure (1–5). NAFLD is an emerging hepatic illness related to obesity, dyslipidemia, and insulin resistance (5). The estimated worldwide prevalence of NAFLD and NASH range from 6.3% to 33% and 3% to 5%, respectively (6).

Choline is an essential nutrient that is required for neurotransmitter synthesis, methyl-group metabolism, cell-membrane structure and signaling, and lipid transport (7–9). Phosphatidylcholine (PC) is synthesized in all nucleated mammalian cells via the CDP–choline pathway; this pathway uses choline as the initial substrate, and thus it mainly depends on dietary choline intake (7–10). The liver is unique in that it possesses a second pathway for PC synthesis; phosphatidylethanolamine *N*-methyltransferase (PEMT) converts phosphatidylethanolamine (PE) to PC via 3 sequential methylations using *S*-adenosylmethionone

[1] Supported by Canadian Institutes of Health Research (CIHR) grant 106613, Natural Sciences and Engineering Research Council of Canada grant 386652, and Alberta Innovates-Biosolutions. R.L.J. is a CIHR New Investigator.

[2] Authors disclosures: A. Al Rajabi, G. S. F. Castro, R. P. da Silva, R. C. Nelson, A. Thiesen, H. Vannucchi, D. F. Vine, S. D. Proctor, C. J. Field, J. M. Curtis, and R. L. Jacobs, no conflicts of interest.

[6] Abbreviations used: ABCA1, ATP-binding cassette subfamily A, member 1; ALT, alanine aminotransferase; BSEP, bile salt export pump; CD-68, cluster of differentiation-68; CE, cholesteryl ester; COL1A1, collagen type I α 1; CYP7A1, cholesterol 7 α-hydroxylase; CYP8B1, sterol 12 α-hydroxylase; FC, free cholesterol; F4/80, EGF-like module containing, mucin-like, hormone receptor-like sequence 1; HF, high-fat; HF$^{-/-}$, *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet; HF$^{+/+}$, *Pemt*$^{+/+}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet; HFCS, high-fat, choline-supplemented; HFCS$^{-/-}$, *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet supplemented with choline; *Ldlr*$^{-/-}$, low-density lipoprotein receptor knockout; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NOX2, NADPH oxidase 2; NTCP, sodium taurocholate cotransporting polypeptide; OATP1, organic anion transporting polypeptide 1; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine *N*-methyltransferase; PL, phospholipid; ROS, reactive oxygen species; SHP, small heterodimer partner; SOAT1, sterol *O*-acyltransferase 1; SR-B1, Scavenger receptor class B type 1; UCP2, mitochondrial uncoupling protein 2.

* To whom correspondence should be addressed. E-mail: rjacobs@ualberta.ca.

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as the methyl donor (11–13). Importantly, PEMT is the only de novo pathway for choline biosynthesis in mammals.

When fed an unpurified diet, *Pemt*$^{-/-}$ mice have a normal liver morphology with minimally affected concentrations of hepatic PC and PE (9,14,15). However, when fed a high-fat (HF) diet for 3 wk, *Pemt*$^{-/-}$ mice develop hepatic steatosis attributable to impaired TG secretion (16). In a separate study, *Pemt*$^{-/-}$ mice fed an HF diet for 10 wk presented with hepatomegaly, steatohepatitis, and a decreased PC:PE ratio (17). Furthermore, *Pemt*$^{-/-}$ mice developed end-stage liver failure within 3 d of consuming a choline-deficient diet attributable to a significant decrease in the PC:PE ratio (18–20).

Jacobs et al. (17) reported recently that *Pemt*$^{-/-}$ mice were protected from HF-diet–induced obesity and insulin resistance that could be reversed by supplementing the diet with choline. When the *Pemt*$^{-/-}$ mice were bred with the low-density lipoprotein receptor knockout (*Ldlr*$^{-/-}$) mice, the resulting *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice had decreased hepatic VLDL secretion and were protected from atherosclerosis when fed an HF–cholesterol diet (21). The initial purpose of this study was to determine whether the reduction in atherosclerosis in the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice could be modulated by dietary choline supplementation. Contrary to what we predicted, HF-diet–fed *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice presented with severe weight loss and liver damage within 3 wk. To explain this phenomenon, we evaluated the choline requirement in the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice. Choline supplementation prevented weight loss in the mice lacking *Pemt* and *Ldlr*. Furthermore, we show that increased choline consumption prevented steatohepatitis and liver failure, but not TG accumulation, in *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice fed an HF diet. Our data provide a novel association between choline availability and hepatic cholesterol metabolism in a context of NAFLD.

Materials and Methods

All procedures were conducted in accordance with the Canadian Council on Animal Care Guidelines and Policies with approval by the University of Alberta Health Sciences Animal Care and Use Committee. Male mice (n = 8–10 per group) were maintained on an unpurified diet (PICO Laboratory Rodent Diet 20; LabDiet). At 10–12 wk of age, *Pemt*$^{+/+}$/*Ldlr*$^{-/-}$ (HF$^{+/+}$) and half of the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ (HF$^{-/-}$) mice were fed an HF diet with normal (1.3 g/kg) choline. The remaining *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice were fed an HF diet supplemented (5 g/kg) with choline (HFCS$^{-/-}$ mice). The HF diet (F6535; Bio-Serv) contained 60% of calories from fat and 1% cholesterol (wt:wt), and mice consumed food ad libitum for 16 d. Choline bitartrate (C1629; Sigma-Aldrich) was used as the source of choline. A pilot study was performed to investigate the long-term consequences of HF-diet feeding in the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice. The HF$^{-/-}$ mice lost >20% body weight, and the feeding trial was terminated after only 21 d (data not shown). On examination, the HF$^{-/-}$ mice presented with severe hepatomegaly and NASH.

All mice were food deprived for 12 h before being killed by exsanguination under isoflurane anesthesia. Plasma was collected and frozen at −80°C. The liver was snap frozen in liquid nitrogen and then stored at −80°C, or preserved in 10% phosphate-buffered formalin, pH 7.0. The extent of steatosis, hepatocyte ballooning, and both lobular and portal inflammation were graded by a pathologist using the Brunt criteria (22). Plasma alanine aminotransferase [ALT (Biotron Diagnostics)] and bile acids (Trinity Biotech) were determined using a commercially available kit. Total phospholipids (PLs), TG, free cholesterol (FC), and cholesteryl ester (CE) were measured by GLC (20,23). The extraction and quantification of PLs and choline-related compounds were performed according to the method by Xiong et al. (24). RNA extraction, cDNA preparation, and qPCR analysis were performed as described previously (25). A standard curve was used to calculate mRNA level relative to the control gene, 18S.

Data are reported as means ± SDs. Data were subjected to Bartlett's test for homogeneity of variances; unequal variances were stabilized by log transformation. Data were compared using 1-factor ANOVA, followed by a Tukey's post hoc test. Histologic grading was compared using a Kruskal-Wallis ANOVA of rank, followed by Dunn's multiple-comparison test. The level of significance was set at $P < 0.05$ in all analyses.

Results

In an attempt to explain the sensitivity of the *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice to the HF diet, we performed a 16-d feeding trial. By day 16 of feeding, the HF$^{-/-}$ mice weighed significantly less than the HF$^{+/+}$ and HFCS$^{-/-}$ mice (**Fig. 1***A*). In addition, HFCS$^{-/-}$ mice had lowered liver weight (6.7 ± 0.3% body weight) compared with HF$^{-/-}$ (10.2 ± 0.7% body weight), but remained higher when compared with the HF$^{+/+}$ (4.0 ± 0.2% body weight) mice.

Histologic examination of the liver revealed the development of severe steatosis, as indicated by enlarged lipid droplets in the liver that coincided with hepatomegaly, hepatocytes ballooning, and inflammation in HF$^{-/-}$ mice compared with HF$^{+/+}$ mice (**Fig. 2***A*, *B*). The size of the lipid droplets and hepatocyte inflammation were reduced in the HFCS$^{-/-}$ mice (Fig. 2*A*, *B*) compared with HF$^{-/-}$ mice. Plasma ALT activity, a measure of liver damage, was 6.4-fold higher in HF$^{-/-}$ mice compared with HF$^{+/+}$ mice; choline supplementation significantly reduced the increase in plasma ALT caused by *Pemt* deletion (Fig. 2*C*). mRNA markers of macrophages [EGF-like module containing, mucin-like, hormone receptor-like sequence 1 (*F4/80*) and cluster of differentiation (*CD*)-*68*], oxidative stress [mitochondrial uncoupling protein 2 (*Ucp2*) and NADPH oxidase 2 (*Nox2*)], and fibrosis [collagen type I α 1 (*Col1a1*)] were elevated in HF$^{-/-}$ compared with HF$^{+/+}$ and HFCS$^{-/-}$ mice (Fig. 2*D*). Hepatic TG (**Fig. 3***A*), CE (Fig. 3*B*), and FC (Fig. 3*C*) concentrations were significantly higher in HF$^{-/-}$ compared with HF$^{+/+}$ mice (Fig. 3*A*-*C*). Hepatic CE and FC concentrations were normal in the HFCS$^{-/-}$ mice, but hepatic TG concentrations remained elevated compared with HF$^{+/+}$ mice (Fig. 3*A*-*C*). Interestingly, HF$^{-/-}$ and HFCS$^{-/-}$ mice had significantly lowered plasma TG (Fig. 3*D*), CE (Fig. 3*E*), and FC (Fig. 3*F*) compared with HF$^{+/+}$ mice. Plasma CE and TG were lower in HF$^{-/-}$ than HFCS$^{-/-}$ mice. HF$^{-/-}$ mice had a

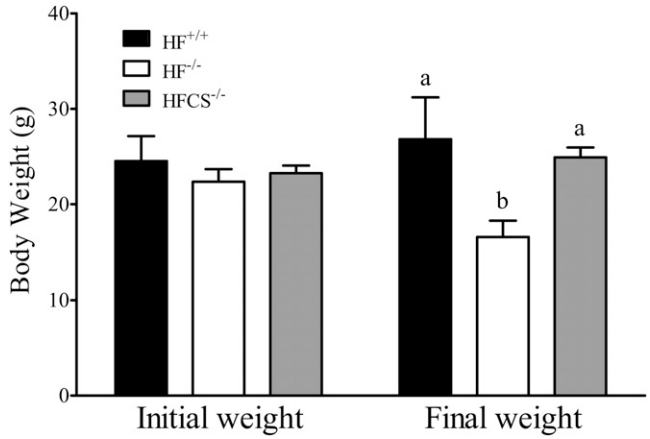

FIGURE 1 Initial and final body weight in HF$^{+/+}$, HF$^{-/-}$, and HFCS$^{-/-}$ mice. Values are means ± SDs; n = 4–5 per group. Groups without a common letter differ, $P < 0.05$. HF$^{+/+}$, *Pemt*$^{+/+}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet; HF$^{-/-}$, *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet; HFCS$^{-/-}$, *Pemt*$^{-/-}$/*Ldlr*$^{-/-}$ mice fed a high-fat diet supplemented with choline; *Ldlr*, LDL receptor; *Pemt*, phosphatidylethanolamine *N*-methyltransferase.

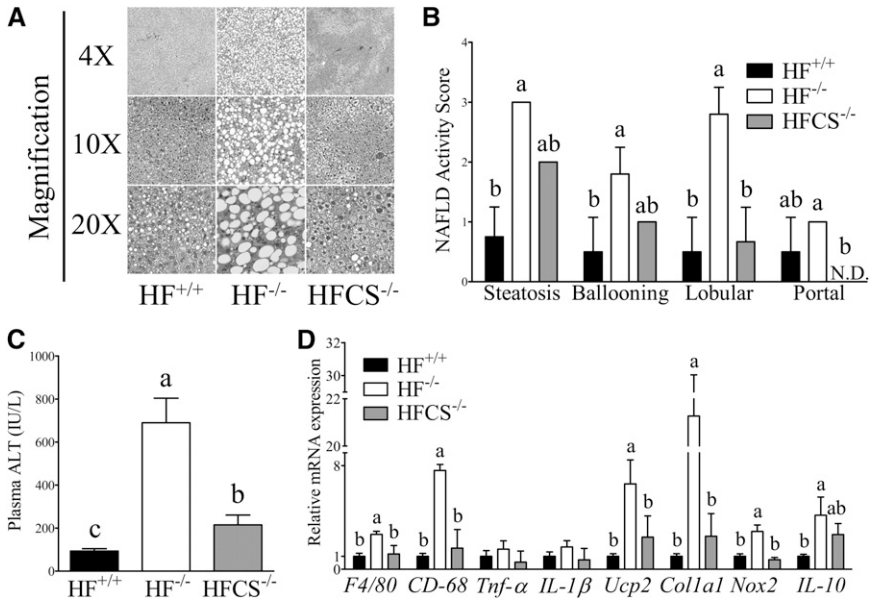

FIGURE 2 Liver histology, NAFLD activity, plasma ALT, and mRNA assessment of liver damage in $HF^{+/+}$, $HF^{-/-}$, and $HFCS^{-/-}$ mice. Liver histology: hematoxylin and eosin staining (*A*). Representative images from each treatment group are shown. NAFLD histologic activity scores (*B*). Plasma ALT concentrations (*C*). mRNA markers of liver damage (*D*). Results were normalized to 18S. In (*B-D*), values are means ± SDs. Groups without a common letter differ, $P < 0.05$. ALT, alanine aminotransferase; *CD-68*, cluster of differentiation-68; *Col1a1*, collagen type I α 1; *F4/80*, EGF-like module containing, mucin-like, hormone receptor-like sequence 1; $HF^{+/+}$, $Pemt^{+/+}/Ldlr^{-/-}$ mice fed a high-fat diet; $HF^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet; $HFCS^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet supplemented with choline; *IL-1β*, interleukin-1β; *IL-10*, interleukin-10; *Ldlr*, LDL receptor; NAFLD, nonalcoholic fatty liver disease; *Nox2*, NADPH oxidase 2; N.D., not detectable; *Pemt*, phosphatidylethanolamine *N*-methyltransferase; *Tnf-α*, tumor necrosis factor-α; *Ucp2*, mitochondrial uncoupling protein 2.

significant reduction in hepatic lysophosphatidylcholine, glycerophosphocholine, PC, and PE compared with $HF^{+/+}$ mice (**Table 1**). $HFCS^{-/-}$ mice had higher lysophosphatidylcholine, PC, and PE compared with $HF^{-/-}$ mice, but these metabolites remained lower compared with the $HF^{+/+}$ mice. The concentration of hepatic lysophosphatidylethanolamine was reduced in $HF^{-/-}$ mice compared with both $HF^{+/+}$ and $HFCS^{-/-}$ mice. The concentration of sphingomyelin and choline and the PC:PE ratio was lower in both $HF^{-/-}$ and $HFCS^{-/-}$ mice compared with $HF^{+/+}$ mice (Table 1).

The expression of ATP-binding cassette subfamily A, member 1 (*Abca1*), *Sr-b1* (scavenger receptor class B type 1), multidrug resistant protein 2, and sterol *O*-acyltransferase 1 (*Soat1*) was greater in $HF^{-/-}$ mice compared with $HF^{+/+}$ mice (**Table 2**). Choline supplementation normalized the expression of *Abca1*, *Sr-b1*, and *Soat1* but not multidrug resistant protein 2 expression caused by *Pemt* deletion. The concentration of 3-hydroxy-3-methylglutaryl-CoA reductase mRNA was not altered by experimental treatments. Plasma bile acids were elevated in $HF^{-/-}$ mice (122 ± 27.4 μmol/L) compared with $HF^{+/+}$ mice (22.5 ± 4.1 μmol/L). The concentration of plasma bile acids in $HFCS^{-/-}$ mice (12.8 ± 2.9 μmol/L) did not significantly differ from $HF^{+/+}$ mice. The hepatic mRNA concentrations of cholesterol 7 α-hydroxylase (*Cyp7a1*), sterol 12 α-hydroxylase (*Cyp8b1*), organic anion transporting polypeptide 1 (*Oatp1*), sodium taurocholate cotransporting polypeptide (*Ntcp*), bile salt export pump (*Bsep*), and small heterodimer partner (*Shp*) genes were lower in $HF^{-/-}$ compared with $HF^{+/+}$ mice. Choline supplementation normalized the abundance of *Cyp7a1*, *Ntcp*, *Bsep*, and *Shp* genes, increased the expression of *Oatp1* compared with $HF^{-/-}$, and increased the expression of *Cyp8b1* compared with the other 2 groups (Table 2).

Discussion

The current research has provided strong evidence that *Pemt* deletion increases choline requirements in $HF^{-/-}$ mice. $HF^{-/-}$ mice lost significant body weight and liver function, although

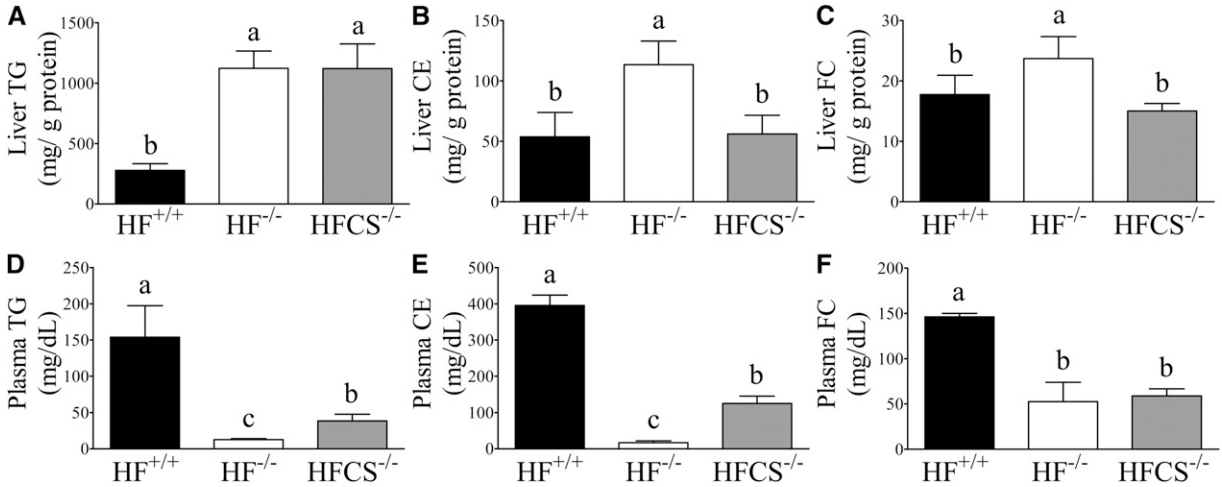

FIGURE 3 Liver and plasma CE, FC, and TG in $HF^{+/+}$, $HF^{-/-}$, and $HFCS^{-/-}$ mice, showing hepatic lipid concentrations (*A-C*) and plasma lipid concentrations (*D-F*). In (*A-F*), values are means ± SDs. Groups without a common letter differ, $P < 0.0001$. CE, cholesteryl ester; FC, free cholesterol; $HF^{+/+}$, $Pemt^{+/+}/Ldlr^{-/-}$ mice fed a high-fat diet; $HF^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet; $HFCS^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet supplemented with choline; *Ldlr*, LDL receptor; *Pemt*, phosphatidylethanolamine *N*-methyltransferase.

TABLE 1 Liver choline and phospholipid concentrations in $HF^{+/+}$, $HF^{-/-}$, and $HFCS^{-/-}$ mice[1]

	$HF^{+/+}$	$HF^{-/-}$	$HFCS^{-/-}$
Choline, *μg/mg liver*	0.017 ± 0.001[a]	0.009 ± 0.002[b]	0.008 ± 0.001[b]
LPC, *μg/mg liver*	0.32 ± 0.03[a]	0.11 ± 0.01[c]	0.18 ± 0.03[b]
LPE, *μg/mg liver*	0.19 ± 0.02[a]	0.14 ± 0.01[b]	0.20 ± 0.01[a]
SM, *μg/mg liver*	1.45 ± 0.29[a]	0.78 ± 0.04[b]	0.72 ± 0.01[b]
GPC, *μg/mg liver*	0.11 ± 0.02[a]	0.06 ± 0.01[b]	0.08 ± 0.01[a,b]
PC, *μg/mg liver*	15.0 ± 0.57[a]	5.78 ± 0.63[c]	9.70 ± 1.42[b]
PE, *μg/mg liver*	9.98 ± 0.63[a]	5.71 ± 0.77[c]	8.54 ± 0.93[b]
PC:PE ratio	1.51 ± 0.07[a]	1.02 ± 0.09[b]	1.16 ± 0.10[b]

[1] Values are means ± SDs; n = 4–5 per group. For a variable, means in a row with superscripts without a common letter differ, $P < 0.05$. GPC, glycerophosphocholine; $HF^{+/+}$, $Pemt^{+/+}/Ldlr^{-/-}$ mice fed a high-fat diet; $HF^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet; $HFCS^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet supplemented with choline; *Ldlr*, LDL receptor; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; *Pemt*, phosphatidylethanolamine *N*-methyltransferase; SM, sphingomyelin.

they consumed the recommended dietary amount of choline (1.3 g choline/kg diet). $HF^{-/-}$ mice had significantly lower hepatic PC and PE concentrations; in addition, they developed hepatomegaly and hepatic inflammation, accumulated more hepatic TG, CE, and FC, and presented a 6.4-fold increase in plasma ALT compared with $HF^{+/+}$ mice. Choline supplementation successfully prevented weight loss and a decline in liver function, and attenuated inflammation by normalizing hepatic cholesterol concentrations and metabolism. In addition, choline supplementation increased hepatic PC and PE but did not affect TG concentrations in PEMT-deficient mice. In addition to an elevated plasma ALT, the expression of multiple genes implicated in hepatic inflammation and liver damage (*F4/80*, *CD-68*, *Ucp2*, *Nox2*, and *Col1a1*) was induced in $HF^{-/-}$ mice. During increased oxidative stress brought about by hepatic steatosis, UCP2 partially uncouples ATP synthesis from mitochondrial respiration, which may limit the formation of mitochondrial reactive oxygen species (ROS) (26). NOX2 is a key subunit of NADPH oxidase and is also involved in oxidative stress, whereas COL1A1 is a marker of fibrosis. Choline supplementation normalized the expression of those genes (Fig. 2*D*).

TABLE 2 Hepatic expression of genes involved in cholesterol and bile acid metabolism in $HF^{+/+}$, $HF^{-/-}$, and $HFCS^{-/-}$ mice[1]

	Relative mRNA expression		
Gene	$HF^{+/+}$	$HF^{-/-}$	$HFCS^{-/-}$
Abca1	1.00 ± 0.10[b]	1.54 ± 0.20[a]	0.97 ± 0.37[b]
Sr-b1	1.00 ± 0.12[b]	1.63 ± 0.29[a]	1.16 ± 0.28[b]
Soat1	1.00 ± 0.21[b]	6.58 ± 1.30[a]	1.54 ± 1.37[b]
HMG-CoA-Red	1.00 ± 0.14[a]	1.25 ± 0.28[a]	1.21 ± 0.31[a]
Cyp7a1	1.00 ± 0.25[a]	0.04 ± 0.02[b]	0.80 ± 0.39[a]
Cyp8b1	1.00 ± 0.42[b]	0.03 ± 0.01[c]	2.01 ± 0.40[a]
Oatp1	1.00 ± 0.23[a]	0.003 ± 0.002[c]	0.42 ± 0.01[b]
Ntcp	1.00 ± 0.10[a]	0.17 ± 0.05[b]	1.07 ± 0.16[a]
Bsep	1.00 ± 0.18[a]	0.39 ± 0.07[b]	1.10 ± 0.15[a]
Mdr2	1.00 ± 0.11[b]	1.55 ± 0.19[a]	1.83 ± 0.55[a]
Shp	1.00 ± 0.34[a]	0.38 ± 0.23[b]	1.25 ± 0.11[a]

[1] Data are means ± SDs; n = 4–5 per group. Relative mRNA expression was normalized to 18S expression. For a variable, means in a row with superscripts without a common letter differ, $P < 0.05$. *Abca1*, ATP-binding cassette subfamily A, member 1; *Bsep*, bile salt export pump; *Cyp7a1*, cholesterol 7 α-hydroxylase; *Cyp8b1*, sterol 12 α-hydroxylase; $HF^{+/+}$, $Pemt^{+/+}/Ldlr^{-/-}$ mice fed a high-fat diet; $HF^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet; $HFCS^{-/-}$, $Pemt^{-/-}/Ldlr^{-/-}$ mice fed a high-fat diet supplemented with choline; *HMG-CoA-Red*, 3-hydroxy-3-methylglutaryl-CoA reductase; *Ldlr*, LDL receptor; *Mdr2*, multidrug resistant protein 2; *Ntcp*, sodium taurocholate cotransporting polypeptide; *Oatp1*, organic anion transporting polypeptide 1; *Pemt*, phosphatidylethanolamine *N*-methyltransferase; *Shp*, small heterodimer partner; *Soat1*, sterol *O*-acyltransferase 1; *Sr-b1*, Scavenger receptor class B type 1.

Jacobs et al. (17) reported that $Pemt^{-/-}$ mice were protected from HF (60% of calories as fat, 0% cholesterol, 1.3 g choline/kg diet) diet–induced obesity and insulin resistance. This protection was reversed when the HF diet was supplemented with choline. In a separate study, HF [40% of calories as fat, 1.25% cholesterol (wt:wt), 3.43 g choline/kg diet] diet–fed $Pemt^{-/-}/Ldlr^{-/-}$ mice were dramatically protected from atherosclerosis (21). In both studies (17,21), mice did not suffer excessive weight loss throughout the feeding period. The data from the current study indicate that the $Pemt^{-/-}/Ldlr^{-/-}$ mice are susceptible to the hepatic consequences of HF diet feeding and, as such, have a higher requirement for dietary choline.

PC accounts for >50% of PLs in most mammalian membranes and is crucial for cellular integrity, differentiation, and proliferation (27,28). It is well established that a decreased hepatic PC:PE ratio is related to NAFLD progression in mice (17,29). In humans, a reduced hepatic PC:PE ratio was observed in patients with NASH (20). The appropriate distribution of PC and PE is essential for cellular integrity and for transport of molecules across intracellular membranes (30,31). When this ratio is decreased, leakage of cellular contents into the extracellular space activates resident Kupffer cells, leading to increased inflammation, impaired mitochondrial respiration, and hepatocyte injury (20,29). In the current study, the $HF^{-/-}$ mice presented with lower hepatic PC and PC:PE ratio compared with the $HF^{+/+}$ mice (Table 1); the consequent reduction in VLDL secretion (21) increased hepatic TG and lowered plasma TG in these mice (Fig. 3*A*, *D*). Surprisingly, hepatic and plasma TG remained elevated in the $HFCS^{-/-}$ mice (Fig. 3*A*, *D*), which could be attributed to the failure of choline supplementation to completely reverse the reduction in PC concentrations or increase the PC:PE ratio (Table 1). However, the progression of NAFLD from steatosis to NASH was prevented in $HFCS^{-/-}$ mice (Fig. 2*B*).

The $HF^{-/-}$ mice had elevated hepatic CE and FC compared with $HF^{+/+}$ mice (Fig. 3*B*, *C*). Similarly, $HF^{-/-}$ mice presented an induced expression of 2 cholesterol transport genes, *Abca1* and *Sr-b1*, as well as a 5.6-fold increase in the expression of *Soat1*, the gene coding for acyl-CoA:cholesterol acyltransferase that converts cholesterol to CE (Table 2). The expression of cholesterol metabolism-related genes (Table 2) and CE and FC concentrations (Fig. 3*B*, *C*) was normalized in $HFCS^{-/-}$ mice. From these novel findings, we proposed that elevated concentrations of hepatic free cholesterol play a significant role in the progression of NAFLD. Cholesterol is a substrate for bile acid synthesis; as such, an excess of free cholesterol in the $HF^{-/-}$ mice could increase bile acid formation. In support of this hypothesis, plasma bile was elevated 4.4-fold in the $HF^{-/-}$ mice; this increase was prevented by choline supplementation. Increased intracellular concentrations of hydrophobic bile acids are believed to play an important role in liver injury by inducing apoptosis or necrosis of hepatocytes (32). Hydrophobic bile acids induce injury to cultured human hepatocytes (33), isolated rat hepatocytes (34), and whole rat liver (35). Through their detergent actions, bile acids may compromise the structural integrity of cell membranes (36), leading to ROS. ROS induce oxidative damage, causing mitochondrial dysfunction, endoplasmic reticulum stress, and cell death (37). Bile acids can also activate Kupffer cells to produce ROS, exacerbating liver injury (38).

To investigate the significance of hepatic free cholesterol in the progression of NAFLD, we measured the expression of genes involved in bile acid synthesis (Table 2). *CYP7A1* is the rate-limiting enzyme for the conversion of cholesterol to bile acids via the classical pathway (39,40). *CYP8B1* controls the ratio of cholic acid-to-chenodeoxycholic acid and thus plays a crucial role in bile acid synthesis via the alternative pathway (41). Both *Cyp7a1*and *Cyp8b1* are subject to a feedback inhibition when bile acids are elevated (42–44). Likewise, *Ntcp* (45,46) and *Oatp1* (47), 2 proteins responsible for the reuptake of bile acids by the liver (47), were dramatically reduced in $HF^{-/-}$ mice. It is possible that the reduction in these bile acid metabolism genes is attributable to increased farnesoid X receptor signaling (42,43,47); however, we observed a reduction in *Shp* and *Bsep* mRNA in the livers of $HF^{-/-}$ mice. SHP feeds back and inhibits its own expression (42,43), which could explain the reduction in *Shp* mRNA levels in $HF^{-/-}$ mice. Diminished *Bsep* expression was reported previously under obstructive cholestasis, characterized by bile acid accumulation in serum and liver, and several other pathophysiologic conditions (48). A reduction in bile acid metabolism genes could also be attributable to the activation of liver X receptor (49). Interestingly, we observed an upregulation of 2 liver X receptor target genes, *Abca1* and *Soat1*, in $HF^{-/-}$ mice (50). Together, the changes in cholesterol and bile acid metabolism in response to *Pemt* deletion and choline supplementation (Table 2) support our hypothesis that elevated hepatic free cholesterol concentrations play a significant role in the progression of NAFLD, potentially via providing the substrate for and increasing hepatic bile acids in $HF^{-/-}$ mice.

In conclusion, $Pemt^{-/-}/Ldlr^{-/-}$ mice require extra dietary choline to maintain a healthy liver. Choline supplementation did not prevent steatosis in the $Pemt^{-/-}/Ldlr^{-/-}$ mice but was able to normalize cholesterol metabolism, which was sufficient in improving liver function and preventing the progression to NASH and liver failure. An abundant single nucleotide polymorphism in the human *PEM*T gene (V175M) is associated with NAFLD; the V175M PEMT is ~40% less active compared with wild-type PEMT. This single nucleotide polymorphism can decrease PC formation and VLDL secretion, leading to hepatic steatosis (51). Our study suggests that people with the V175M mutation may require dietary choline supplementation, especially if they eat a diet high in fat. Our data also suggest that the provision of dietary choline or 1 of its metabolites can maintain liver health by regulating cholesterol metabolism.

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Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial[1,2]

Jeffrey R Wozniak,[3] Anita J Fuglestad,[3] Judith K Eckerle,[4] Birgit A Fink,[3] Heather L Hoecker,[6] Christopher J Boys,[4] Joshua P Radke,[7] Maria G Kroupina,[4] Neely C Miller,[4] Ann M Brearley,[5] Steven H Zeisel,[8] and Michael K Georgieff[4]*

[3]Department of Psychiatry, [4]Department of Pediatrics, and [5]Biostatistical Design and Analysis Center, University of Minnesota Twin Cities, Minneapolis, MN; [6]School of Public Health, Emory University, Atlanta, GA; [7]Fagron Inc., St. Paul, MN; and [8]University of North Carolina at Chapel Hill Nutrition Research Institute, Kannapolis, NC

ABSTRACT

Background: Fetal alcohol spectrum disorders (FASDs) are conditions characterized by physical anomalies, neurodevelopmental abnormalities, and neurocognitive deficits, including intellectual, executive, and memory deficits. There are no specific biological treatments for FASDs, but rodent models have shown that prenatal or postnatal choline supplementation reduces cognitive and behavioral deficits. Potential mechanisms include phospholipid production for axonal growth and myelination, acetylcholine enhancement, and epigenetic effects.

Objective: Our primary goal was to determine whether postnatal choline supplementation has the potential to improve neurocognitive functioning, particularly hippocampal-dependent memory, in children with FASDs.

Design: The study was a double-blind, randomized, placebo-controlled pilot trial in children (aged 2.5–5 y at enrollment) with FASDs (n = 60) who received 500 mg choline or a placebo daily for 9 mo. Outcome measures were Mullen Scales of Early Learning (primary) and the elicited imitation (EI) memory paradigm (secondary).

Results: The administration proved feasible, and choline was well tolerated. Participants received a dose on 88% of enrolled days. The only adverse event linked to choline was a fishy body odor. Choline supplementation improved the secondary outcome (EI) only after immediate recall performance was controlled for, and the outcome was moderated by age. The treatment effect on EI items recalled was significant in the younger participants (2.5- to ≤4.0-y-olds); the young choline group showed an increase of 12–14 percentage points greater than that of the young placebo group on delayed recall measures during treatment. However, there was a marginal baseline difference in delayed item recall between the young choline and placebo groups as well as a potential ceiling effect for item recall, both of which likely contributed to the observed treatment effect. We also observed a trend toward a negative effect of choline supplementation on the immediate EI recall of ordered pairs; the young placebo group showed an increase of 8–17 percentage points greater than that of the choline group during treatment. There was an inverse relation between choline dose (in mg/kg) and memory improvement (P = 0.041); the data suggest that weight-adjusted doses may be a better alternative to a fixed dose in future studies. Limitations included trend-level baseline differences in performance, the post-hoc determination of age moderation, and potential ceiling effects for the memory measure.

Conclusions: This pilot study suggests that an additional evaluation of choline supplementation as an intervention for memory functioning in children with FASDs is warranted. The observed interaction between age and choline's effect on EI suggests that potential sensitive periods should be considered in future work. This trial was registered at clinicaltrials.gov as NCT01149538. *Am J Clin Nutr* 2015;102:1113–25.

Keywords: children, fetal alcohol spectrum disorder, fetal alcohol syndrome, memory, randomized double-blind placebo-controlled trial

INTRODUCTION

Fetal alcohol spectrum disorders (FASDs)[9] represent a profound public health crisis with prevalence estimates as high as 2–5% in the United States and Western Europe (1). Individuals with fetal alcohol syndrome (FAS), which is the most severe form of FASD, have high rates of intellectual impairment (2, 3). Individuals with other FASDs, including partial fetal alcohol syndrome (pFAS) and alcohol-related neurodevelopmental disorder, are seriously affected by deficits in attention, executive functioning, and memory among other skills (4–6). Currently, there have been very few cognitive and behavioral interventions for FASDs (7–9), and there are no biological treatments.

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[2] Supplemental Table 1 and Supplemental Equations *1–7* are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail: jwozniak@umn.edu.

[9] Abbreviations used: CNS, central nervous system; EI, elicited imitation; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; IOM, Institute of Medicine; pFAS, partial fetal alcohol syndrome; REML, restricted maximum likelihood estimation; TMAO, trimethylamine *N*-oxide.

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Preclinical models of FASDs have consistently identified the hippocampus as particularly vulnerable to insult, and numerous experiments revealed memory deficits in animals exposed to alcohol prenatally (10–12). Studies of memory in children with prenatal alcohol exposure also have shown deficits in hippocampus-mediated encoding processes (13, 14). In normally developing animals, choline supplementation during gestation and the early postnatal period enhances performances on measures of cognition including memory (15–17). In animals exposed prenatally to alcohol, there has been strong evidence that dietary choline supplementation prenatally during hippocampal neurogenesis and postnatally, as late as days 21–30 during rapid hippocampal differentiation in the rodent (equivalent to human early childhood), attenuates memory and behavioral deficits that are normally observed (18, 19). Improvements have been seen in cognitive functions and behaviors that rely on the hippocampus including visual-spatial learning, spatial reversal learning, and fear conditioning (20).

At the time of the writing of this article, there were no published human trials of choline supplementation in FASDs to our knowledge. We previously reported on a pilot study that examined the safety and tolerability of choline in children with FASDs ($n = 20$) (21), and in the current study, we report on the results of the completed trial that included the participants from the previous pilot study. The trial enrolled 60 participants with FASDs who were aged 2.5–5 y. The goals of the overall study were to establish the feasibility of long-term choline supplementation in a large sample of children with FASDs and, because of compelling basic science findings, to examine the efficacy of choline as a neurocognitive treatment by specifically targeting behaviors dependent on hippocampal integrity. Thus, we hypothesized that choline would improve performances on a hippocampus-dependent memory task [elicited imitation (EI)] and, more generally, on a test of global cognitive functioning.

TABLE 1
Baseline characteristics of participants who received the allocated intervention[1]

	Choline ($n = 31$)	Placebo ($n = 29$)
Age, y	3.79 ± 0.80[2]	3.92 ± 0.76
Sex, *n* (%)		
M	12 (39)	10 (35)
F	19 (61)	19 (65)
Racial categories, *n* (%)		
White	16 (52)	9 (31)
Black or African American	5 (16)	9 (31)
American Indian/Alaska Native	4 (13)	7 (24)
Asian	1 (3)	1 (4)
More than one race	5 (16)	3 (10)
Ethnic category, *n* (%)		
Hispanic or Latino	1 (3)	1 (3)
Not Hispanic or Latino	29 (94)	27 (93)
Unknown	1 (3)	1 (4)
Dysmorphic facial features, *n* (%)		
Lip (score of 4 or 5)	16 (52)	10 (35)
Philtrum (score of 4 or 5)	13 (42)	9 (31)
Palpebral fissure (≤10th percentile)[3]	21 (68)	20 (69)
≥2 facial features present	20 (65)	17 (59)
Growth deficiency (≤10th percentile), *n* (%)		
Height[3]	4 (13)	0 (0)
Weight	5 (16)	1 (3)
Deficient brain growth (≤10th percentile) OFC,[3] *n* (%)	3 (10)	0 (0)
Alcohol exposure, *n* (%)		
Alcohol confirmed	24 (77)	26 (90)
Alcohol suspected	7 (23)	3 (10)
Drug exposure, *n* (%)		
Other drug exposure suspected	21 (68)	21 (72)
IOM diagnostic category, *n* (%)		
FAS	5 (16)	5 (17)
Partial FAS	15 (48)	11 (38)
ARND	11 (36)	13 (45)
Baseline cognitive-functioning scores[4]		
Mullen Visual Reception	41 ± 12	44 ± 16
Mullen Fine Motor	42 ± 9	40 ± 15
Mullen Receptive Language	41 ± 9	40 ± 12
Mullen Expressive Language	40 ± 8	41 ± 11
Mullen Early Learning Composite	83 ± 14	84 ± 21

[1]ARND, alcohol-related neurodevelopmental disorder; FAS, fetal alcohol syndrome; IOM, Institute of Medicine; OFC, occipital-frontal circumference.

[2]Mean ± SD (all such values).

[3]Data from the study baseline were missing from participants who were uncooperative and from whom an accurate measure could not be obtained for palpebral fissure length (choline: $n = 3$), height (choline: $n = 1$), and OFC (choline: $n = 1$). Data acquired from previous clinical evaluations are included for these participants.

[4]Data were missing for 2 participants (choline: $n = 2$) who were unable to finish testing.

METHODS

The study was a randomized, double-blind, placebo-controlled trial conducted at the University of Minnesota from June 2010 to May 2014. Participants underwent an informed consent process, and all procedures were approved by the University's Institutional Review Board. Additional oversight was provided by the University's clinical trial monitoring program as well as an independent Data Safety Monitoring Board. Choline was administered under the Federal Drug Administration Investigational New Drug application 107085. The trial was registered at clinicaltrials.gov as NCT01149538 on 21 June 2010 before the first participant's enrollment. A complete description of methods and procedures was reported in Wozniak et al. (21).

Subjects

Children with FASDs (aged 2.5–5.0 y at enrollment) were recruited from the University's FASD Clinic and International Adoption Clinic. Sixty children received the allocated intervention (**Table 1**) of whom 85% ($n = 51$) completed the 9-mo study (**Figure 1**).

Exclusion criteria were the presence of another developmental disorder (e.g., autism, Down syndrome), neurologic disorder, traumatic brain injury, or other medical condition that affects the brain. Psychiatric comorbidity, such as attention-deficit hyperactivity disorder or learning disorder, was not exclusionary because comorbidity is common with FASDs (22). All but one participant (a twin born at 36 wk who weighed1360 g) had a birth weight >1500 g.

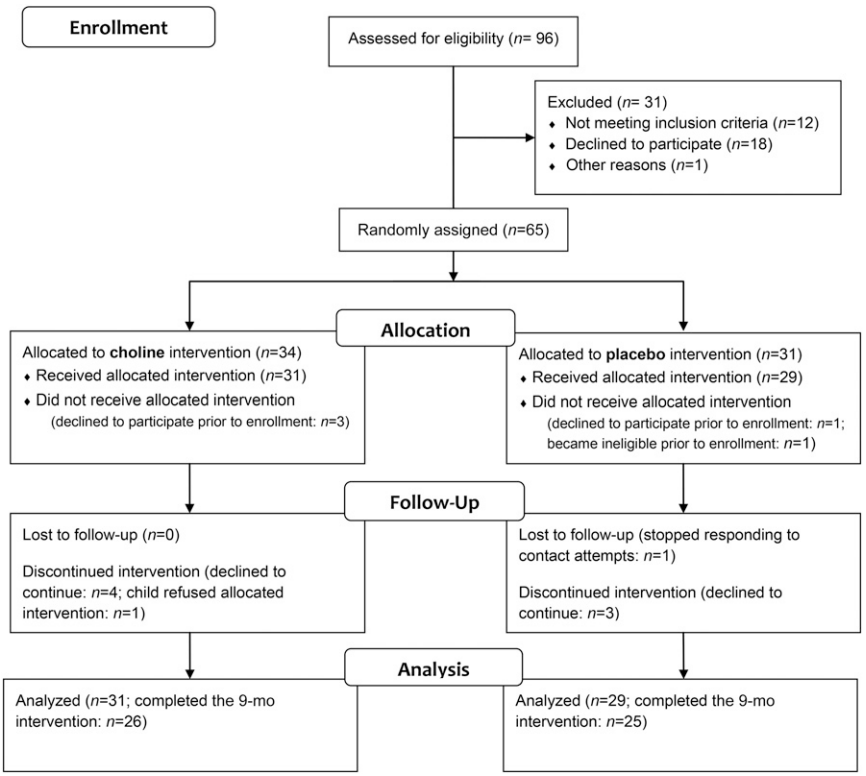

FIGURE 1 Flowchart of the randomized clinical trial of postnatal choline supplementation.

To characterize the sample diagnostically, we applied modified Institute of Medicine (IOM) criteria (23) to the growth, facial dysmorphology, and alcohol-exposure data collected in the clinic and during the baseline visit. Of 60 participants, 10 individuals (17%) met the criteria for FAS; 24 individuals (40%) met criteria for pFAS; and 24 individuals (40%) met criteria for alcohol-related neurodevelopmental disorder (Table 1).

Because IOM criteria do not specifically characterize cognitive functioning, we further applied CDC central nervous system (CNS) criteria for FASDs (24) [see our previous article for details (21)]. Nineteen participants (32%) met the CNS criteria for an FASD diagnosis on the basis of deficient brain growth, whereby 15 subjects (25%) had global cognitive impairment (>2 SDs below the average), and 57 subjects (95%) had deficits of >1 SD in ≥3 domains (e.g., intellectual, language, motor, visual-perceptual, adaptive functioning, and behavioral domains). One participant (2%) was deficient in only one domain. Twenty-six participants (43%) met ≥2 CNS criteria.

Eighty-three percent of subjects ($n = 50$) had confirmed prenatal alcohol exposure, including a self-report by the biological mother or social service records that indicated heavy maternal use during pregnancy. Participants with maternal alcohol use at rank 3 or 4 in the University of Washington diagnostic system (25) were included. Ten participants had unconfirmed alcohol exposure, but alcohol use was suspected, and all 10 subjects had dysmorphic faces and cognitive deficits as previously defined. The 10 subjects met the modified IOM criteria for FAS ($n = 1$) or pFAS ($n = 9$). In 42 cases, other prenatal drug use was suspected. There was no difference in suspected drug use between the 2 treatment arms (Table 1). In all cases, alcohol was the predominant substance of abuse, and alcohol use was extensive.

Procedures

Participants received the supplement daily for 9 mo. The length of the intervention was selected to measure the potential developmental change in response to the treatment and to maintain a feasible daily administration of the experimental agent in preschool-age children, who are a group for whom supplementation can be challenging.

The study was designed to be completed in 2 phases. The primary outcome assessed in the first phase was side effects or adverse events, the results of which have been reported previously (21). The second phase was designed to further evaluate safety and tolerability and to measure the effect of choline on neurocognitive functioning. The primary outcome was an assessment of global cognitive functioning with the use of the Mullen Scales of Early Learning. The secondary outcome was an assessment of hippocampal-dependent function with the use of the EI memory task. Event-related potential data were also collected as an electrophysiological measure of brain functioning; however, event-related potential results are not reported in the current article because they were beyond the scope of the current report.

In-person assessments took place at the University of Minnesota at baseline (before receiving the allocated intervention) and at 6 and 9 mo. Phone visits occurred 2 wk after baseline and then monthly to monitor compliance and adverse events. The Mullen Scales of Early Learning were administered at baseline and at 9 mo. EI was administered at all 3 visits (at baseline and at 6 and 9 mo).

Allocated intervention

Participants were randomly assigned in a one-to-one allocation ratio with the use of preprepared computerized block-randomization schedules by the University's Investigational Drug

Services unit to receive 500 mg choline (1.25 g choline bitartrate) or a placebo daily for 9 mo. A concealed allocation was implemented, and the research team and participants were blinded to group assignments. The allocated intervention was supplied in coded light-blocking foil packets that contained a powdered, fruit-flavored drink mix that was developed for the study. Packet dosages and stability were evaluated with the use of HPLC by an outside laboratory. The dosage was within 0.13% of the target, on average, and stable (within 5.2% of target dosage over the study duration). Parents were instructed to administer 1 dose/d by mixing it with 4 fl oz (118.3 mL) H_2O.

Measures

Feasibility of choline supplementation

Compliance, fidelity, and adverse events were monitored via calendar log sheets, dietary recalls, and serum choline concentrations. Parents used calendar log sheets to document the proportion of the allocated intervention the children consumed each day. If <100% of the drink was consumed, the amount and reason were recorded.

Detailed 24-h food recalls were administered at baseline and at 6 and 9 mo with the use of the automated self-administered 24-h recall system (26) to evaluate the potential confounding influence of changes in dietary choline intake. Dietary data were included only if the parent recalled all meals and snacks from the 24-h period (e.g., data were not included if the parent had no information about the child's intake at school on that day). Numbers of subjects are reported for all dietary intake data. Families were instructed to refrain from adding dietary supplements during the study, which was reinforced at all study visits including phone visits.

Serum choline and betaine concentrations were measured at baseline and at 6 and 9 mo. Parents were asked to administer the allocated intervention 3 h before the scheduled blood draw (venipuncture). Choline and betaine were assayed with the use of liquid chromatography/electrospray ionization–isotope dilution mass spectrometry (27).

A physician completed a physical examination at each in-person visit, which included a review of major organ systems, to assess adverse events. Adverse events were also monitored during monthly phone visits. Changes in body or urine odor were monitored because high serum choline concentrations have been associated with fishy odor that is due to trimethylamine formation (28). For a subsample, plasma was assayed for trimethylamine *N*-oxide (TMAO) with the use of liquid chromatography/electronspray ionization–isotope dilution mass spectrometry (29). The TMAO assay was added midway through the study and was only done on a random subset because of the cost. Compliance problems with the administration of the allocated intervention were also monitored monthly.

Mullen Scales of Early Learning (primary outcome)

The Mullen Scales of Early Learning (30) is a measure of global cognitive development with the use of normative data from birth to 68 mo of age. The measure assesses visual reception, fine motor, receptive language, and expressive language abilities, and yields *t* scores for each of these subtests with a mean ± SD of 50 ± 10 points. Subtest scores are summed and converted to an Early Learning Composite, which is an age-scaled intelligence quotient–like score with a mean ± SD of 100 ± 15 points.

EI (secondary outcome)

The EI paradigm assesses explicit memory ability in preverbal children via the behavioral imitation of action sequences (31, 32). This paradigm is a nonverbal analog to verbal memory report (33) and requires support from the hippocampus (34). The paradigm reflects normal developmental changes in memory ability within the age range of the current study (35), is sensitive to neurodevelopmental disruption (36), and is predictive of later memory abilities in school-age children (37). The task involves sets of toys that are used in event sequences. Each sequence has a theme (e.g., going camping) and incorporates multiple toys that are used in a prescribed sequence of 9 individual actions (e.g., baiting a hook, catching a fish, and setting up a tent).

At each assessment, participants were shown 2 different 9-item sequences. The procedure included a free play period and a recall measure for each sequence. During free play, children were given the toys to manipulate for 2 min. The free play provided a control for spontaneous occurrences of target actions. An experimenter modeled the event sequence twice with narration. The child was directed to recall the event sequence in one of 2 conditions (immediate or delayed). For immediate recall, the child was asked to imitate the sequence after modeling. For delayed recall, the toys were removed for 15 min after which the child was asked to reproduce the sequence. Immediate recall provided a measure of attention to the task and the encoding of items and sequences. Delayed recall provided a measure of hippocampal-dependent long-term memory. For each child, the 2 sequences were drawn from a larger set of available sequences that were, in turn, counterbalanced across conditions (immediate and delayed) and visits.

The production of individual items (e.g., baiting a hook, catching a fish, and setting up a tent) and the correctly ordered pairs of items (i.e., baiting the hook before catching the fish and then setting up the tent) was assessed for both free play and the recall for each condition (immediate and delayed). Sessions were video recorded and scored offline by trained raters. Twenty percent of the videos were coded by multiple raters to ensure reliability (93%). The variables analyzed were the percentage of correct individual items produced (maximum: 9) and the percentage of correctly ordered pairs produced (maximum: 8) for the following 3 conditions: free play, immediate recall, and delayed recall. Only immediate and delayed recall measures were used in the current study. There were no group differences in EI free -play performance.

Statistical analyses

Feasibility and tolerability analyses

The distributions of the compliance log-sheet variables were nonnormal and leptokurtic, and therefore, medians and IQRs are reported. Between-group comparisons of these variables were conducted with the use of Mann-Whitney *U* tests. The distribution of serum TMAO was also nonnormal at the 6- and 9-mo visits, and medians and IQRs for TMAO are reported in addition to the mean value for each visit. For between-group comparisons of categorical variables, Fisher's exact test was used because of small cell sizes. The Freeman-Halton extension of the Fisher's exact test (38) was used for contingency tables that were larger

than 2 × 2. *t* tests were used for between -group comparisons of continuous variables.

Mixed-model specification

Growth curve analyses with the use of linear mixed models were performed to test for treatment differences in growth trajectories (intercepts, which represented baseline differences, and slopes, which represented the differential change over time) for the feasibility and neurocognitive data. The analyses, which modeled fixed effects and random child-specific intercepts, were conducted with the SAS (version 9.4) Proc Mixed procedure (SAS Institute Inc.) with the use of a restricted maximum likelihood estimation (REML). The REML with an estimated df procedure (39) was used because data were not available for all participants at each time point, and the REML yields valid variable estimates with incomplete data without imputing missing data or using list-wise deletion. The variables are estimated under the assumption that the missing data could be ignored (40), which was assumed in the current study. The following 2 types of general linear mixed models (random-effects models) were initially considered: *1*) models with child-specific intercepts only and *2*) models with both child-specific intercepts and child-specific slopes. Models were compared with the use of the Akaike information criterion, which takes into account both the degree of model fit to the data and the model complexity. Intercept-only models were shown to have consistently better Akaike information criterion values than the intercept and slope models did. Longitudinal analyses were conducted as intention-to-treat analyses with all available data from participants who received the allocated treatment (choline: $n = 31$; placebo: $n = 29$) included in the analyses independent of their completion of the study and compliance during the study (Figure 1).

For data collected at 3 visits (e.g., EI memory data), the linear slope term was specified to estimate the growth trajectory across 3 time points (time 0: baseline; time 1: 6-mo visit; time 1.5: 9-mo visit). The intercept represents the estimated value at baseline (time 0) in the growth curves, and the linear slope represents the change in outcome over the time during treatment, with one unit of time along the *x*-axis representing 6 mo of treatment. For data collected at 2 visits (e.g., Mullen Scales), the linear slope term was specified across 2 time points (time 0: baseline; time 1: 9-mo visit).

Curve fit

Before the main effects of treatment were tested, unconditional growth-curve analyses were performed to determine whether the general growth trajectory for each longitudinal outcome was linear or nonlinear (quadratic) regardless of the treatment group (**Supplemental Equation *1***). Unconditional analyses (which did not include the treatment group in the model) gave growth-curve estimates for the entire sample. The appropriate slope (linear or quadratic) was tested in the conditional analyses (with the treatment group added to the analysis) to examine treatment-group differences (**Supplemental Equations *2–6***). All reported longitudinal analyses tested for the linear change unless otherwise specified.

Tests for demographic moderation of main treatment effects

For the neurocognitive data (Mullen Scales and EI), 2 sets of conditional longitudinal analyses were performed to test the treatment effect. First, the main effect of treatment was examined without demographic covariates or moderators (Supplemental Equations *2* and *4*). Second, 3-way interactions between the treatment group and age, race, or FASD diagnosis were examined to test for moderation (i.e., whether the association between treatment and neurocognitive outcomes differed as a function of these subject variables) (Supplemental Equations *3* and *5*). For each significant 3-way interaction, simple slope analyses were completed to evaluate the change in performance over time for each value of the moderator (41).

Assessment of main treatment effects with and without demographic covariates

Variables were included as covariates if there was a difference in the group distribution even after random assignment and if there was a potential association with the outcome measures. Covariates included age, race, and FASD diagnosis. Because dysmorphic facial features, growth deficiency, deficient brain growth, and alcohol exposure form the basis of an FASD diagnosis, these variables were not included again as independent covariates. The remaining demographic characteristics were not included as covariates because they were very closely matched or had no known association with the outcome measures. Analyses are presented with and without the covariates included in the model (Supplemental Equations *5* and *6*). Effect sizes are presented for both the unadjusted (no covariates) and adjusted (with covariates) models.

Immediate EI performance as a covariate

For EI, the hypothesis was that choline would improve the performance on the delayed recall condition because it depends on hippocampal integrity. Choline's effects in preclinical models have been predominantly on the developing hippocampus (18–20). Growth-curve analyses were completed for a delayed performance with the corresponding immediate condition performance included as a covariate in the model (Supplemental Equations *4–6* and **Supplemental Equation *7***). The child's immediate performance represents the ability to attend to the stimuli and encode a sequence and was included in the models to control for the variability introduced by these nondelay–related characteristics of the child's performance.

Effect size

For significant linear slope results, effect sizes (Cohen's *d* values) were determined by first standardizing the change scores (the difference between the estimated mean baseline and 9-mo follow-up scores) by the SD of the raw baseline scores for each treatment group (42). The difference between the standardized change scores for the 2 treatment groups was calculated. Effect sizes for significant moderators were determined by calculating the difference between the effect for the placebo and treatment groups for each value of the moderator.

RESULTS

Feasibility of choline supplementation: compliance, fidelity, and adverse events

Completed log sheets were returned by 95% of participants. Participants reportedly received a partial dose (at least one-quarter)

or a full dose of the allocated intervention on 88% (IQR: 69–96%) of the days in the study. Reported days that participants received a dose did not differ between the 2 arms [choline: median: 87% (IQR: 72–93%); placebo: median: 90% (IQR: 69–96%); $P = 0.306$]. The 24-h dietary recall data revealed no differences in dietary choline intake across the 2 arms at any point (**Table 2**). Significant increases in serum choline (102%) and betaine (106%) concentrations occurred with choline supplementation (Table 2).

A fishy odor was the only adverse event that occurred differentially in the choline arm during treatment (**Table 3**). This odor was due to trimethylamine formation by gut bacteria; trimethylamine is oxidized in the liver to form TMAO. During treatment, serum TMAO concentrations reached 22-times higher in the choline arm than in the placebo arm (Table 2; 6 mo). A fishy odor was episodically noticeable to parents (mostly when changing clothes, bathing, or toileting) but was not noticeable to the research assistant who administered the outcome measures. Physical examination results, including height, weight, and blood pressure, remained consistent for both groups throughout the duration of the study (Table 2).

Mullen Scales of Early Learning (primary outcome measure)

Intercept (baseline difference) and linear slope (change over time) results were examined to test the main effect of treatment on the Mullen Scales (Supplemental Equation *2*). None of the intercept or linear slope results reached significance, which indicated that there were no differences between the 2 treatment arms before treatment or during treatment of the Mullen Early Learning Composite or of any of the subscales (Table 2). None of the 3-way interactions used to test moderation for the main effect of treatment on the linear slope reached significance for the Mullen Scales (Supplemental Equation *3*).

The Mullen Early Learning Composite was correlated (with age controlled for) with EI delayed performance for items (partial $r = 0.56$, $P < 0.001$) and ordered pairs (partial $r = 0.47$, $P < 0.001$) at baseline but not at the 9-mo visit ($P > 0.17$ for all). In other words, the Mullen scales and EI measures similarly reflected the participant's level of functioning at baseline, but the 2 measures were differentially responsive to the intervention.

EI (secondary outcome measure)

Intercept and linear slope results were examined to test the main effect of treatment on the growth trajectory of EI (items and ordered pairs; Supplemental Equation *4*). For the whole sample, none of the intercept or linear slope results reached significance for delayed recall (items or ordered pairs), which indicated that there were no differences between the 2 arms (choline compared with placebo) before treatment or during treatment of EI items (estimated means for choline at baseline: 74%; at 6 mo: 81%; and at 9 mo: 84%; estimated means for the placebo at baseline: 79%; at 6 mo: 83%; and at 9 mo: 85%). There were no differences for ordered pairs (estimated means for choline at baseline: 41%; at 6 mo: 52%; and at 9 mo: 58%; estimated means for the placebo at baseline: 44%; at 6 mo: 52%; and at 9 mo: 57%). Thus, for the whole sample, there was not a significant effect of choline on EI delayed memory performance).

Race and FASD diagnosis as potential moderators of choline's effects on EI

To examine whether the treatment effect on EI delayed recall was moderated by race or FASD diagnosis, 3-way interactions for the linear slope were examined (Supplemental Equation *5*). None of the analyses reached significance, which showed that the treatment effect on delayed recall did not differ between children of different races or with different FASD diagnoses.

Age as a moderator of choline's effects on EI

Because preclinical data showed that early choline supplementation in prenatally exposed animals is associated with greater cognitive improvements than later supplementation is (43), we hypothesized that age would be an important factor in the human response to choline supplementation [the potential interaction with age was discussed in our earlier article on the first pilot study (21)]. To examine whether the treatment effect on delayed EI performance was moderated by age, 3-way interactions between the treatment arm, age at baseline (as a continuous variable), and either the intercept or linear slope were examined on EI delayed performance (items and ordered pairs). Immediate (nondelayed) performance was included as a covariate (Supplemental Equation *5*). The intercept was significant for items [$\gamma = 11.60$ (95% CI: 0.23, 22.98), $t(114) = 2.02$, $P = 0.046$] but not for ordered pairs [$\gamma = 3.91$ (95% CI: −6.74, 14.56), $t(118) = 0.73$, $P = 0.469$]. The linear slope was also significant for items [$\gamma = -10.76$ (95% CI: −20.41, −1.10), $t(83.1) = -2.21$, $P = 0.030$] but not for ordered pairs [$\gamma = -4.28$ (95% CI: −13.59, 5.03), $t(84.5) = -0.91$, $P = 0.363$]. In summary, the group difference (choline compared with placebo) in the rate of EI improvement over time differed depending on the child's age.

Age as a moderator of choline's effects on EI with the use of split-age groups

To more easily illustrate the moderating role of age on the treatment effect and to gain an understanding of effect sizes, the sample was split into 2 groups on the basis of the median age as follows: a younger group ($n = 30$; placebo: $n = 13$; choline: $n = 17$) consisting of 2.5- to ≤4.0-y-olds and an older group consisting of >4.0–5.0-y-olds ($n = 30$; placebo: $n = 16$; choline: $n = 14$). Three-way interactions were examined between the treatment arm, age group, and either the intercept or linear slope for delayed EI performance (items and ordered pairs; **Supplemental Table 1** and Supplemental Equation *5*). In the model for items, there was a trend-level 3-way interaction between the treatment group, age group, and linear slope [$\gamma = -14.75$ (95% CI: −30.38, 0.88), $t(84.9) = -1.88$, $P = 0.064$] but not for the intercept [$\gamma = 15.52$ (95% CI: −3.20, 34.25), $t(109) = 1.64$, $P = 0.103$]. For ordered pairs, there was a trend-level 3-way interaction between the treatment group, age group, and linear slope [$\gamma = -13.68$ (95% CI: −28.89, 1.52), $t(89.1) = -1.79$, $P = 0.077$] but not for the intercept [$\gamma = 8.95$ (95% CI: −8.43, 26.34), $t(117) = 1.02$, $P = 0.310$]. As in the previous evaluation, age appeared to play a role in the response to choline in terms of the rate of improvement in EI delayed performance.

Figure 2 shows the estimated growth curves for the treatment arms by age group for EI delayed recall (items and ordered

TABLE 2
Results of growth-curve analyses that examined treatment-group differences in dietary choline intake, serum choline, physical examination results, and Mullen Early Learning Scales by treatment arm[1]

	Unadjusted values				Growth-curve analyses, $\gamma \pm$ SE; P	
	Choline (n = 31)		Placebo (n = 29)			
	n	Mean ± SD	n	Mean ± SD	Estimated intercept, choline vs. placebo	Estimated linear slope, choline vs. placebo
Dietary choline, mg/d					−11.29 ± 23.87; 0.637	−6.87 ± 21.58; 0.751
Baseline	30	177 ± 88	23	195 ± 60		
6 mo	18	231 ± 99	21	221 ± 104		
9 mo	23	194 ± 86	18	223 ± 86		
Serum choline, μM					−0.25 ± 0.82; 0.766	4.77 ± 0.75; <0.0001*
Baseline	22	6.53 ± 1.62	23	7.20 ± 1.51		
6 mo	21	13.18 ± 4.15	17	7.38 ± 1.68		
9 mo	20	13.23 ± 4.19	18	7.16 ± 1.68		
Serum betaine, μM					−0.78 ± 8.60; 0.928	28.70 ± 5.69; <0.0001*
Baseline	22	42.96 ± 16.64	23	48.91 ± 9.79		
6 mo	21	85.27 ± 39.07	17	50.92 ± 17.45		
9 mo	20	88.83 ± 50.85	18	50.38 ± 17.26		
TMAO,[2] μM					1.89 ± 17.81; 0.916	−98.34 ± 42.84; 0.033*
Baseline	7	2.87 ± 1.94	6	0.98 ± 0.66		
6 mo	7	70.73 ± 68.94	6	3.22 ± 1.51		
9 mo	5	29.34 ± 21.57	5	4.94 ± 7.39		
Height z score					−0.49 ± 0.23; 0.038*	−0.06 ± 0.06; 0.322
Baseline	30	−0.35 ± 0.89	29	0.12 ± 0.86		
6 mo	20	−0.20 ± 0.85	18	0.29 ± 0.76		
9 mo	25	−0.19 ± 0.86	22	0.35 ± 0.92		
Weight z score					−0.43 ± 0.27; 0.114	0.04 ± 0.04; 0.319
Baseline	31	−0.14 ± 1.18	29	0.29 ± 0.81		
6 mo	26	0.11 ± 1.21	24	0.32 ± 0.80		
9 mo	26	0.12 ± 1.25	25	0.31 ± 0.80		
Blood pressure, mm Hg					2.46 ± 2.48; 0.323	−1.60 ± 2.46; 0.515
Systolic						
Baseline	27	103 ± 11	28	101 ± 9		
6 mo	23	102 ± 8	24	100 ± 12		
9 mo	23	100 ± 8	24	100 ± 7		
Diastolic					2.44 ± 2.71; 0.368	−3.83 ± 2.56; 0.137
Baseline	27	63 ± 14	28	61 ± 10		
6 mo	23	61 ± 12	24	62 ± 7		
9 mo	23	60 ± 8	24	64 ± 9		
Mullen Early Learning Scales score						
Early Learning Composite					−1.82 ± 4.73; 0.701	−0.36 ± 3.09; 0.908
Baseline	29	83.2 ± 13.7	29	84.3 ± 21.4		
9 mo	26	87.1 ± 16.4	25	89.6 ± 21.6		
Visual Reception					−3.26 ± 3.69; 0.381	−0.30 ± 2.98; 0.920
Baseline	29	41.2 ± 11.8	29	44.4 ± 16.2		
9 mo	26	43.5 ± 10.8	25	47.0 ± 13.9		
Fine Motor					1.34 ± 3.30; 0.69	−0.67 ± 2.69; 0.805
Baseline	29	42.0 ± 9.3	29	40.1 ± 15.0		
9 mo	26	44.4 ± 10.1	25	43.3 ± 15.8		
Receptive Language					0.44 ± 2.88; 0.879	−0.04 ± 2.19; 0.984
Baseline	29	40.6 ± 9.4	29	39.8 ± 12.4		
9 mo	26	42.2 ± 10.8	25	41.8 ± 12.3		
Expressive Language					−1.31 ± 2.57; 0.614	0.08 ± 2.72; 0.978
Baseline	29	40.3 ± 8.5	29	41.2 ± 10.8		
9 mo	26	42.6 ± 10.3	25	44.2 ± 10.3		

[1]Longitudinal analyses with linear mixed models with the use of restricted maximum likelihood estimations were used to compare differences in growth curves between treatment groups (Supplemental Equation *2*). For the growth-curve analyses, the estimated intercept column contains comparisons of baseline values (time 0), and the estimated linear slope column contains comparisons of change over time including baseline (time 0), 6 mo (time 1), and 9 mo (time 1.5). For Mullen Scales, the time included baseline (time 0) and 9 mo (time 1). *$P < 0.05$.

[2]TMAO, trimethylamine *N*-oxide. The slope term reported for TMAO was quadratic and represented a significant nonlinear change. Median (IQR) values for TMAO (μM) were as follows—at baseline: choline group, 2.90 μM (0.60–4.60 μM); placebo group, 1.00 μM (0.28–1.60 μM); at 6 mo: choline group, 38.3 μM (13.50–150.70 μM); placebo group, 3.30 μM (2.08–4.05 μM); and at 9 mo: choline group, 40.40 μM (6.25–46.90 μM); placebo group, 1.50 μM (1.15–10.45 μM).

TABLE 3
Number of participants reporting symptoms at baseline and number reporting new symptoms (adverse events that were not present at baseline) at least once during the course of treatment[1]

	Choline (n = 31)	Placebo (n = 29)	P (Fisher's exact test)
Administration problems with the supplement, n (%)			
Baseline	—	—	—
New symptoms during treatment	13 (42)	12 (41)	1.000
General health, n (%)			
Baseline	7 (23)	3 (10)	−0.302
New symptoms during treatment	8 (28)	5 (18)	0.530
Skin, n (%)			
Baseline	9 (29)	15 (52)	0.113
New symptoms during treatment	4 (14)	4 (14)	1.000
Ear, nose, and throat, n (%)			
Baseline	1 (3)	3 (10)	0.346
New symptoms during treatment	1 (4)	0 (0)	1.000
Cardiovascular, n (%)			
Baseline	2 (7)	2 (7)	1.000
New symptoms during treatment	1 (3)	0 (0)	1.000
Respiratory, n (%)			
Baseline	5 (16)	10 (35)	0.139
New symptoms during treatment	5 (17)	4 (14)	1.000
Gastrointestinal, n (%)			
Baseline	14 (45)	12 (41)	0.800
New symptoms during treatment	9 (31)	7 (25)	0.770
Fishy body odor, n (%)			
Baseline	0 (0)	0 (0)	1.000
New symptoms during treatment	15 (52)	1 (4)	<0.001*
Genitourinary, n (%)			
Baseline	6 (19)	2 (7)	0.257
New symptoms during treatment	3 (10)	8 (29)	0.103
Musculoskeletal, n (%)			
Baseline	3 (10)	7 (24)	0.175
New symptoms during treatment	0 (0)	0 (0)	1.000
Neurologic, n (%)			
Baseline	15 (48)	11(38)	0.446
New symptoms during treatment	6 (21)	4 (14)	0.730
Allergy, n (%)			
Baseline	7 (23)	10 (35)	0.394
New symptoms during treatment	0 (0)	2 (7)	0.237
Other, n (%)			
Baseline	13 (42)	9 (31)	0.431
New symptoms during treatment	8 (28)	13 (46)	0.175

[1]During treatment, sample sizes were as follows: choline group: n = 29; placebo group: n = 28. *$P < 0.05$.

pairs) while controlling for immediate performance. There was a marginal intercept (baseline) difference between treatment arms and age groups for individual items during the delayed EI condition whereby the young age group, particularly the young choline group, performed lower by chance. This difference in intercepts was not likely due to dietary choline because there was no difference in dietary choline intake at baseline between the young choline group (35% of whom met adequate intake) and the young placebo group (40% of whom met adequate intake) (P = 0.807).

During treatment, the largest improvement in delayed EI performance was in the young choline group. Post hoc analyses revealed significant differences in the simple slopes for both delayed items and ordered pairs between treatment groups (choline compared with placebo) for the young-age group but not for the old-age group (**Table 4**). The simple slope values estimated the change over 6 mo (from times 0 to 1). The change over 9 mo of treatment was computed as 1.5 times the simple slope. For delayed items, the young choline group showed an increase of 21% over 9 mo of treatment compared with 7% in the young placebo group (Table 4). For delayed ordered pairs, the change was 28% in the young choline group compared with 16% in the young placebo group (Table 4). Effect sizes were large for both outcome measures in the young group.

Evaluation of demographic covariates

Race and FASD diagnosis were examined as potential confounding variables in the model with age as a moderator to determine whether the association between the treatment group and linear slope in the young group was altered by these variables (Supplemental Equation *6*). With race and FASD diagnosis included as covariates, the adjusted effect size for the linear slope in the young group for delayed EI items was d = 0.58 (unadjusted effect size: d = 0.54) and, for delayed EI ordered pairs, was d = 0.42 (unadjusted effect size: d = 0.50).

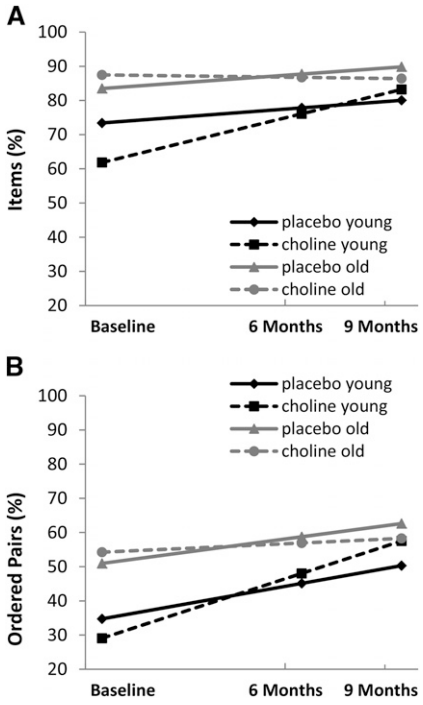

FIGURE 2 Treatment effect on elicited imitation delayed performance was moderated by age for items [slope: $\gamma = -14.75$ (95% CI: −30.38, 0.88), $t(84.9) = -1.88$, $P = 0.064$] and ordered pairs [slope: $\gamma = -13.68$ (95% CI: −28.89), 1.52, $t(89.1) = -1.79$, $P = 0.077$]. The largest improvement in elicited imitation delayed performance occurred in the young choline group (2.5- to ≤4.0-y-olds). (A) Percentages of individual items recalled. (B) Percentages of ordered pairs recalled. Choline: $n = 30$ (young: $n = 16$; old: $n = 14$); placebo: $n = 29$ (young: $n = 13$; old: $n = 16$).

Alternate analysis without controlling for immediate EI performance

The 3-way interaction between the age group, treatment group, and growth curve for delayed EI performance was also examined without controlling for immediate recall performance (Supplemental Equation *3*). Results did not reach significance for any of the growth-curve variables for the delayed performance of items [intercept: $\gamma = 10.51$ (95% CI: −10.98, 32.01), $t(105) = 0.97$, $P = 0.334$; slope: $\gamma = -12.46$ (95% CI: −28.56, 3.63), $t(98.3) = -1.54$, $P = 0.128$] or ordered pairs [intercept: $\gamma = 0.86$ (95% CI: −19.11, 20.84), $t(115) = 0.09$, $P = 0.931$; slope: $\gamma = -7.50$ (95% CI: −23.73, 8.37), $t(98.8) = -0.94$, $P = 0.351$]. In other words, choline's effect of improving delayed EI performance was evident only when nondelay characteristics of the child's performance were controlled for.

Additional analyses of immediate EI performance

Growth trajectories for immediate EI performance are presented by age group and treatment arm in **Figure 3** (Supplemental Equation *3*). Choline was not associated with improvement in the immediate condition for items [intercept: $\gamma = -11.06$ (95% CI: −32.31, 10.19), $t(105) = -1.03$, $P = 0.304$; slope: $\gamma = 3.94$ (95% CI: −13.19, 21.08), $t(86.6) = 0.46$, $P = 0.649$]. There was a trend toward significance in the 3-way interaction for ordered pairs in the immediate condition (intercept: $\gamma = -19.14$ (95% CI: −40.43, 2.15), $t(119) = -1.78$, $P = 0.078$; slope: $\gamma = 17.23$ (95% CI: −0.97, 35.42), $t(93.2) = 1.88$, $P = 0.063$]. Post hoc analyses revealed a significant difference in the simple slopes for immediate ordered pairs between treatment groups (choline compared with placebo) for the young-age group but not for the old-age group (Table 4). The young choline group showed less improvement for ordered pairs, with an increase of 13% over 9 mo compared with 30% in the young placebo group.

Last, to put these results in context, immediate and delayed performances were correlated at the baseline visit (items: partial $r = 0.59$, $P < 0.001$; ordered pairs: partial $r = 0.60$, $P < 0.001$) and at 6 mo (items: partial $r = 0.61$, $P < 0.001$; ordered pairs: partial $r = 0.55$, $P = 0.001$) but not at 9 mo (items: partial $r = 0.15$, $P = 0.322$; ordered pairs: partial $r = 0.26$, $P = 0.074$) while controlling for age. EI delayed and immediate performances were correlated at baseline and 6 mo, but the 2 measures were differentially responsive to the intervention and were no longer correlated at 9 mo.

Average daily choline dose

The association between the average daily choline dose and EI delayed recall was examined in the choline arm. To estimate the mean choline dose received throughout the study, the full dose (500 mg) was corrected for the percentage of days participants received any supplement on the basis of parent-report log sheets. The corrected dose was divided by the child's weight at baseline to yield the average daily choline dose received per kilogram of body weight (mg/kg).

Because of the interaction between the treatment arm and age on EI performance, age was included as a covariate in the dosage analyses. EI immediate recall performance was also included as a covariate (Supplemental Equation *7*). Linear slope results were significant for the choline dose (mg/kg) on EI delayed recall for items [$\gamma = -0.82$ (95% CI: −1.60, −0.04), $t(34.9) = -2.13$, $P = 0.041$] but not for ordered pairs [$\gamma = -0.30$ (95% CI: −1.10, 0.49), $t(36.6) = -0.77$, $P = 0.446$]. Intercept results for the choline dose (mg/kg) did not reach significance for EI items ($P = 0.152$) or for ordered pairs ($P = 0.343$). **Figure 4** depicts this linear association between the dose (divided into quartiles) and EI delayed performance. Subjects in the lowest quartile (i.e., the lowest mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) showed greater improvement of delayed recall for items (21%) than subjects in the highest quartile did (−2%).

Finally, the association between the choline dose and presence of fishy odor was examined. The prevalence of fishy odor was greater in the highest quartile for choline dose (100% of subjects reported a fishy odor at some point during the 9 mo) than in the lower 3 quartiles for choline dose (42% of subjects reported a fishy odor) ($P = 0.020$). There were no differences in the presence of a fishy odor between the lowest 3 quartiles for choline dose (**Figure 5**).

DISCUSSION

This pilot study represents an initial evaluation of the potential efficacy of choline as a cognitive intervention in FASDs. As in our previous study (21), choline had high tolerability and was associated with no serious adverse events at 500 mg/d in 2–5-y-olds with FASDs. The study evaluated choline's effects on cognition in a randomized, double-blind, placebo-controlled trial. Age-dependent improvements were seen on a hippocampus-dependent memory task. In this small pilot sample, younger participants

TABLE 4
Simple slope results by age group for performance on the elicited imitation delayed condition[1]

	Choline (n = 30), $\gamma \pm$ SE	Placebo (n = 29), $\gamma \pm$ SE	t test [$t(28)$, P]	Effect size, d
Delayed condition				
Items				
Young	14.24 ± 3.84	4.43 ± 4.04	−2.41, 0.023	0.54
Old	−0.71 ± 3.98	4.23 ± 3.90	1.21, 0.235	—
Ordered pairs				
Young	18.97 ± 3.65	10.39 ± 4.00	−2.18, 0.038	0.50
Old	2.69 ± 3.79	7.79 ± 3.73	1.31, 0.201	—
Immediate condition				
Items				
Young	8.48 ± 4.23	13.72 ± 4.41	1.18, 0.125	—
Old	2.59 ± 4.36	3.89 ± 4.24	0.29, 0.386	—
Ordered pairs				
Young	8.75 ± 4.45	20.01 ± 4.80	2.36, 0.013	−0.46
Old	11.46 ± 4.61	5.50 ± 4.46	−1.27, 0.107	—

[1]The simple slope was used to estimate the change in delayed performance (%) per 6-mo unit of treatment. The change over 9 mo of treatment can be computed as 1.5 times the change per 6 mo of treatment.

(2.5- to ≤4.0-y-olds) showed greater improvement than older participants (>4.0–5.0-y-olds) did, although there are caveats to interpreting these findings as will be discussed. Young participants in the choline arm showed an increase of 12–14 percentage points greater than in the placebo arm in long-delay memory after 9 mo of supplementation, which was a potentially meaningful improvement. Although we could not characterize the clinical significance of this memory improvement (there are no normative standards for this measure), we do know that an EI performance change is expected in this age range (35), and an EI improvement has implications for future cognitive ability. For example, in one longitudinal study, EI performance at 20 mo of age predicted ≤37% of the variance in explicit memory skill at 6 y of age (37).

In the current study, the effect of choline was seen in the secondary outcome measure (EI delayed memory performance) but not in the primary outcome measure (global cognitive ability). Note that, although EI was the secondary outcome measure, it was considered from the start to be a critical outcome measure because of choline's presumed effects on hippocampal development [see Wozniak et al. (21)]. Cognitive deficits are common in FASDs even when a patient's intelligence quotient is average (44), which suggests that individual neural systems (e.g., hippocampus) may be the most-appropriate targets for an intervention rather than global cognition. The hippocampus is heavily interconnected with other systems (45, 46), and its integrity is critical to the development, functioning, and organization of other domains. Future studies may examine downstream effects of choline on other domains affected in FASDs (e.g., attention, executive function, and behavior regulation).

The observed interaction between choline's effect on memory and younger age was consistent with the potential underlying mechanisms of choline and with existing preclinical data. Prenatally, choline affects neurogenesis, thereby contributing to increased cell proliferation and decreased apoptosis in the hippocampus (47, 48). Postnatal choline may affect synaptogenesis as well as continued hippocampal growth (49), which is rapid during the first 2 y of life and slower thereafter (50). In humans, the hippocampus continues to develop into the fourth year of life (51). In preclinical models, both early supplementation (postnatal days 11–20) and late supplementation (postnatal days 21–30) attenuate cognitive deficits from prenatal alcohol with an advantage for early supplementation (43). The current human results suggest that the specific benefits for delayed sequential memory in FASDs are evident in the first 2–3 y of life, but our results were less conclusive for older children; we observed

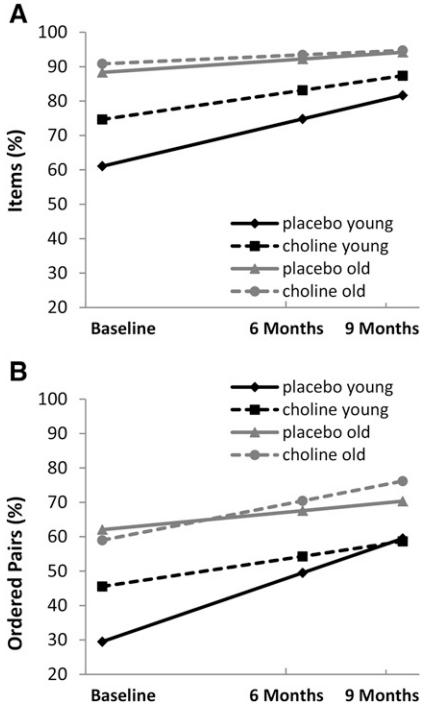

FIGURE 3 Treatment effect on elicited imitation immediate performance. Choline was not associated with the immediate score for items [intercept: $\gamma = -11.06$ (95% CI: −32.31, 10.19), $t(105) = -1.03$, $P = 0.304$; slope: $\gamma = 3.94$ (95% CI: −13.19, 21.08), $t(86.6) = 0.46$, $P = 0.649$]. A trend was seen for immediate ordered pairs [intercept: $\gamma = -19.14$ (95% CI: −40.43, 2.15), $t(119) = -1.78$, $P = 0.078$; slope: $\gamma = 17.23$ (95% CI: −0.97, 35.42), $t(93.2) = 1.88$, $P = 0.063$]. (A) Percentages of individual items recalled. (B) Percentages of ordered pairs recalled. Choline: $n = 30$ (young: $n = 16$; old: $n = 14$); placebo: $n = 29$ (young: $n = 13$; old: $n = 16$).

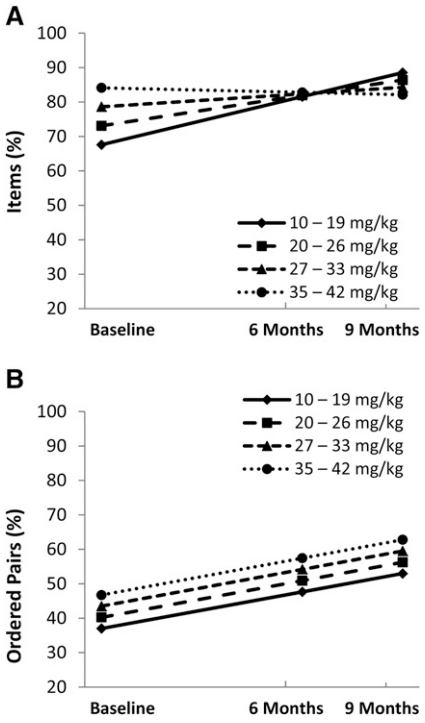

FIGURE 4 Lower daily dose of choline was associated with a greater treatment effect of choline for elicited imitation delayed items [slope: $\gamma = -0.82$ (95% CI: −1.60, −0.04), $t(34.9) = -2.13$, $P = 0.041$) (A) but not for ordered pairs [slope: $\gamma = -0.30$ (95% CI: −1.10, 0.49), $t(36.6) = -0.77$, $P = 0.446$] (B). The daily dose was not associated with the intercept for elicited imitation delayed items ($P = 0.152$) or for ordered pairs ($P = 0.343$). Choline group ($n = 25$)—10–19 mg/kg: $n = 6$; 20–26 mg/kg: $n = 6$; 27–33 mg/kg: $n = 7$; and 35–42 mg/kg: $n = 6$.

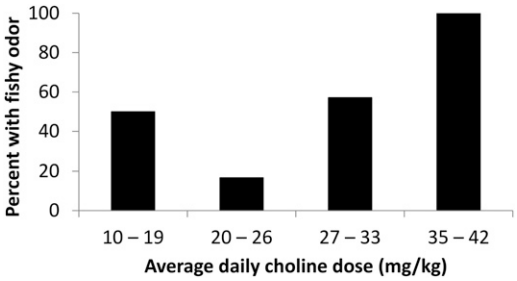

FIGURE 5 Prevalence of fishy body odor was greater in the highest quartile for the choline dose than in the lower 3 quartiles for the choline dose ($P = 0.020$; Fisher's exact test). There were no differences in the presence of a fishy odor between the lowest 3 quartiles for the choline dose. Choline group ($n = 25$)—10–19 mg/kg: $n = 6$; 20–26 mg/kg: $n = 6$; 27–33 mg/kg: $n = 7$; and 35–42 mg/kg: $n = 6$.

a potential ceiling effect in the EI data from the 4–5-y-olds (this was also evident in the younger group) that may have masked treatment effects in the older group. Also, we reiterate that the initial random assignment was not stratified by age; instead, the sample was evaluated for age interactions and was eventually split by age after data collection. For these reasons, an additional examination of choline's potential in 4–5-y-olds may be warranted in future studies.

There are other important caveats to consider. Despite random assignment, there was a significant interaction between age and treatment group ($P = 0.046$), with the young choline group having slightly lower delayed EI performance than the other groups did for items at baseline. The regression to the mean could have contributed to the young choline group showing the largest improvement as opposed to the effect being purely a treatment effect. Another caveat to consider is that item scores were in the 80–90% correct range at the final study visit, which suggested a potential ceiling effect. Together, these factors likely contributed to the observed treatment effect. In a future choline study, the task difficulty could be increased to better evaluate the full potential range of choline's effects.

In the current data, the effect of choline on EI delayed performance depended on controlling for the child's concurrent EI immediate performance, which we believed to be largely a function of the child's attention and initial encoding. There is some evidence in the literature that prenatal choline supplementation has the potential to improve certain aspects of attention (52). The relation between postnatal choline supplementation and attentional capacity in the context of prenatal alcohol exposure is less clear. Choline was expected to improve long-term memory storage and retrieval processes that were measured in the delayed EI condition because choline's mechanisms of action are in the hippocampus and choline typically improves long-delay memory. This was the observed pattern for the recall of individual items. Choline's effects on immediate memory were harder to predict on the basis of the existing literature, but there was some reason to believe that choline could also improve it. In fact, choline did not affect EI immediate performance for items but did improve delayed EI performance for items, which suggested that the effect of choline supplementation is specific to long-delay memory and that controlling for immediate performance may be warranted. However, for EI delayed ordered pairs, the results were more complex. Post hoc analyses suggested that choline may have a negative effect on immediate memory for ordered pairs. Although both treatment arms showed an improvement in immediate performance for ordered pairs during the 9 mo of the study, choline supplementation slightly attenuated this growth for ordered pairs. Thus, choline's effects may be multifaceted, and future studies will need to carefully assess for unexpected changes of this type in nondelay aspects of memory performance.

Data from the current study may influence future choline dosing in studies of children with FASDs. The adequate intake is 200 mg for ages 1–3 y and 250 mg for ages 4–8 y (53). On average, children with FASDs consume insufficient amounts of choline (54). In the current study, the 500-mg dose was selected to bring all participants to sufficiency, to provide supplementation, and to keep amounts in the tolerable range of 1000 mg/d (53). The 500-mg dose substantially raised free serum choline and betaine concentrations. Many subjects in the choline arm (52%) experienced an adverse event of a fishy odor. This event occurred across the dosage range for body weight (mg/kg) but was universal (100%) at the highest dosage. The dosage data showed an inverse relation with memory performance, but there are caveats to consider. Differential doses were not assigned. Rather, because the allocated dose was universal, the individual dosage varied as a function of body weight and compliance (the majority of variance was due to body weight). The measure with which dosage was most associated (EI delayed items) approached a ceiling at baseline and at 9 mo. This effect may have exaggerated the inverse relation between the dose and treatment response. There was no relation between the dose and delayed EI ordered pairs score (for which there was no ceiling effect).

For these reasons, the observed relation between the dosage and outcomes needs to be considered tentative and replicated accordingly. Nonetheless, these data, together with the side-effect data, suggest that supplementation with choline beyond the recommended adequate intake for treatment purposes should take into account the child's weight.

The only adverse event that occurred differentially in the choline arm was a fishy odor. The odor was from trimethylamine, which is formed when choline becomes available to gut bacteria (28). Trimethylamine is converted to TMAO in the liver. We observed significant elevations in serum TMAO concentrations in the choline arm. In rodent models, increased plasma concentrations of TMAO have been suggested as a potential contributor to atherosclerosis (55). Atherosclerosis-prone (apolipoprotein E–negative) mice fed choline or TMAO showed greater aortic root atherosclerotic plaque (56). TMAO concentrations are also associated with acute cardiovascular events in cardiac patients (56, 57). However, it is not known whether TMAO "has a direct effect on pathogenesis, is an epiphenomenal biomarker, or is a precursor to a more direct effector" (58). One study in hamsters showed an inverse relation between plasma TMAO and atherosclerosis (59). Furthermore, fish is a rich source of trimethylamine (60), but dietary fish intake is associated with decreased risk of cardiovascular disease (61). Practically speaking, smaller choline doses given multiple times per day (instead of a single bolus) will reduce or eliminate trimethylamine formation, thereby allowing for the potential management of this adverse effect in future studies.

Additional studies are needed to determine the optimal dosage that improves memory performance and minimizes the fishy odor and TMAO increase. Longitudinal studies will determine the permanency of choline's effects. Furthermore, the minimum adequate length of treatment has yet to be established because the current study tested only the 9-mo duration as a starting point in this line of research.

In conclusion, this pilot study suggests that an additional evaluation of choline as a potential intervention for memory functioning may be warranted in children with FASDs. The results of the trial are encouraging because, to our knowledge, there have been no other intervention studies that have shown similar effects in FASDs nor are there other promising biological interventions ready for human clinical trials.

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The Addition of Choline to Parenteral Nutrition

ALAN L. BUCHMAN

Intestinal Rehabilitation and Transplant Center, Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Choline is a quaternary amine endogenously synthesized from the amino acid methionine or absorbed via the portal circulation. It is ubiquitous in the diet, although it has a greater presence in organ meats. Choline is an essential component of all cell membranes, and has been considered a required dietary nutrient since 1998 by the US Institute of Medicine's Food and Nutrition Board. Choline is necessary for DNA repair, mediated by its role as a methyl donor. It also serves as the precursor for the neurotransmitter acetylcholine. Evidence has accumulated that hepatic steatosis, which occurs during parenteral nutrition therapy, develops as a result of choline deficiency because endogenous production of choline from parenterally infused methionine is deficient. In addition, memory deficits and skeletal muscle abnormalities have been described, and choline deficiency appears to activate cellular apoptosis. Provision of intravenous choline ameliorates hepatic steatosis associated with parenteral nutrition infusion.

Choline deficiency has been described in the guinea pig, mouse, rat, hamster, rabbit, pig, chicken, quail, duck, dog, trout, cow, rhesus monkey, and baboon, with development of cirrhosis described in the rat as well as nonhuman primates.[1] Parenteral nutrition (PN)-associated liver disease is probably a misnomer, and would be better termed *intestinal failure-associated liver disease*. Patients with the least residual intestine and worst residual absorptive capacity are those who are most likely to die, often from intestinal failure-associated liver disease.[2] In one center in Paris, France, the prevalence of chronic cholestasis (defined as increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST], or alkaline phosphatase to greater than 1.5 times the upper limits of normal for >6 mo), was 55% after 2 years and 72% after 6 years among 90 patients, and the prevalence of complicated liver disease (defined as the presence of portal hypertension, portal fibrosis, biopsy-proven cirrhosis, total serum bilirubin concentration >3.5 mg/dL, or hepatic encephalopathy) was greater than 26% after 2 years of nutrition support and 50% after 8 years[3] (Figure 1*A* and *B*). Liver failure accounted for 22% of the patient deaths.

Metabolic Function

Choline is a water-soluble, lipotropic, quaternary amine that is an essential structural component of cell membranes, the neurotransmitter acetylcholine, and phospholipid biosynthesis, where it is integral to the synthesis of very low density lipoprotein necessary for normal triglyceride exportation from the liver, and is a significant source for methyl groups necessary for methylation reactions (along with vitamin B_{12} and folate).

Choline deficiency activates cellular apoptosis.[4–6] This may result in part owing to defective cellular repair mechanisms as illustrated by the observation by Zeisel et al[6] of an increased number of liver hepatocytes containing fragmented DNA, among other morphologic and biochemical changes associated with apoptosis. In fact, hepatocytes die from apoptosis when placed in a choline-deficient medium.[4,7,8] Choline also is involved in lipid transport and transmembrane signaling. The accumulation of 1,2-diacylglycerol, with a resultant prolongation of protein kinase C activation, also appears to be associated with apoptosis.[6]

Although most body stores are found in the form of phospholipid-bound choline, it is decreased plasma-free choline concentration that has been associated with the development of hepatic abnormalities. Important metabolites of choline include betaine, phosphocholine, glycerophosphocholine, and lysophosphatidylcholine (Figure 2).

Since its discovery in 1862 and until 1998, choline had not been considered an essential part of the diet because it can be synthesized in the liver and other organs from the sequential methylation of phosphatidylethanolamine. In 1998, the US Institute of Medicine's Food and Nutrition Board declared choline an essential nutrient based on more contemporary research findings. An adequate intake (AI) as well as an upper limit for dietary choline intake were established. The AI was 550 mg/day for adult men and 425 mg/day for adult women, and the upper limit was 3 g/day.[9] Dietary lecithin (phosphatidylcholine) is the usual source of choline, although patients who require PN will have limited absorption capabilities.

Abbreviations used in this paper: AI, adequate intake; PN, parenteral nutrition.

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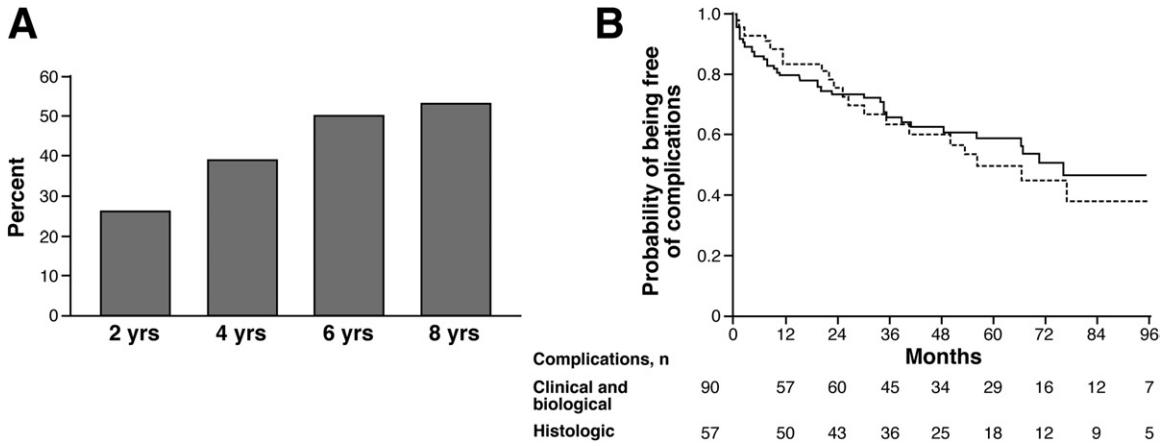

Figure 1. (*A*) The prevalence of complicated liver disease (extensive portal fibrosis or cirrhosis; total serum bilirubin concentration >3.5 mg/dL for at least 1 month; presence of ascites, portal hypertension, hepatic encephalopathy; or a factor V concentration <50% of normal). Adapted from Cavicchi et al.[3] (*B*) Probability of being free of clinical or biological complicated home PN-related liver disease (*solid line*) in 90 patients with permanent intestinal failure and probability of being free of histologic complicated home PN-related liver disease (*dashed line*) in a subgroup of 57 patients who underwent liver biopsy. The probability of developing complicated clinical or biological home PN-related liver disease was 26% (confidence interval [CI], 17%–35%) at 2 years, 39% (CI, 28%–50%) at 4 years, 50% (CI, 37%–63%) at 6 years, and 53% (CI, 39%–67%) at 8 years. The probability of developing a severe histologic lesion (extensive fibrosis or cirrhosis) was 20% (CI, 9%–31%) at 2 years, 35% (CI, 21%–49%) at 4 years, 45% (CI, 29%–61%) at 6 years, and 56% (CI, 37%–75%) at 8 years. Reprinted with permission from Cavicchi et al.[3]

Choline is ubiquitous in the diet, and deficiency in free living individuals, even those on vegan diets, has not been reported outside of specific research settings where a choline-deficient diet was administered. However, in the patient with intestinal failure, choline bioavailability from the diet is decreased markedly as a result of malabsorption. Some dietary choline is degraded by intestinal bacteria to dimethylamines and trimethylamines before absorption.[10] Choline that survives this degradation is absorbed via an active transport-mediated process.[11] Dietary phosphatidylcholine (lecithin) also can be hydrolyzed to free choline by the pancreatic enzymes A_1, A_2, and B. Absorbed free choline then is transported to the liver via the portal vein drainage system.[12]

Orally ingested nutrients generally are absorbed readily from the intestines and shunted to the liver for metabolism via the portal circulation (the first-pass effect). However, when nutrients are infused intravenously, they are

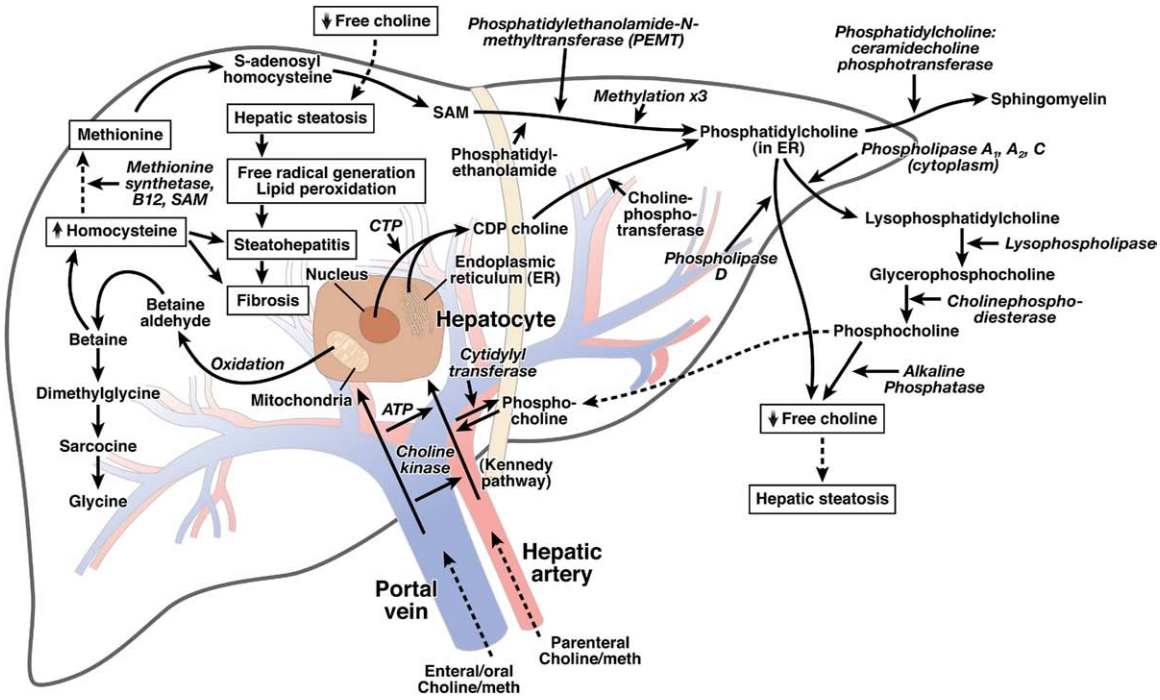

Figure 2. Hepatic choline metabolism.

not delivered to the liver via the portal vein initially, but via the hepatic artery after passing through the heart. The variation in nutrient assimilation may affect nutrient metabolism and downstream metabolic products. When methionine, a precursor for choline that normally is supplied in PN, is infused systemically, cysteine, similar to choline, a downstream metabolic product of the hepatic transsulfuration pathway, was virtually undetectable even in normal volunteers.[13] When methionine was infused enterally in those same volunteers, plasma cysteine concentrations were slightly lower than when consumed with a meal, but substantially greater than that which resulted from systemic methionine infusion. This landmark investigation showed that the hepatic transsulfuration pathway is impaired when substrate is provided via the systemic rather than the portal circulation. The observation of Stegnik and Besten[13] was later observed in patients who required parenteral feeding.[14]

Reliable Assessment for Deficiency and Toxicity

Plasma-free choline concentration may be measured by high-pressure liquid chromatography and gas chromatography–mass spectrometry.[15–17] Recently, a chemiluminescent assay was developed that uses automated hospital equipment.[18] The normal plasma-free choline concentration is 10–15 nmol/mL.[9,19–25] Toxicity has been described with a plasma-free choline concentration greater than 200 nmol/mL.[26]

Clinical Manifestations of Choline Deficiency

Choline deficiency in human beings results in hepatic aminotransferase abnormalities and hepatic steatosis.[24,25,27,28] This is owing to deficient very low density lipoprotein synthesis, with a resultant decrease in triglyceride transport out of the liver.[29,30] Skeletal muscle dysfunction with increased serum creatine phosphokinase also has been observed.[31] Choline deficiency induces DNA damage and apoptotic pathways in these cells,[4,5,32] which may account for the release of hepatic and skeletal muscle enzymes into the bloodstream. Memory abnormalities also have been described.[33] Growth and developmental abnormalities and hemorrhagic nephropathy have been described in animals.

The Role of Choline Deficiency in the Development of PN-Associated Liver Disease

Buchman et al[34] found that plasma-free choline concentration was below normal in more than 80% of mostly adult patients, ages 45.1 ± 24.3 years, who had required home PN for a mean of 5.5 years. A significant inverse relationship was observed between plasma-free choline concentration and both ALT and AST levels. Misra et al[35] found the same in older children (Figure 3). On the other hand, plasma phospholipid-bound choline (mostly phosphatidylcholine) was normal in 83% of adults and children who required long-term PN.[34] Red blood cell free choline concentration was normal. A minimal amount of free choline was found in the intravenous lipids that patients received (24 ± 6 nmol/mL in 20% Intralipid; Fresenius Kabi, Stockholm, Sweden). Plasma-free choline concentrations were significantly below normal despite provision of the choline precursor methionine in the PN solution. Plasma methionine concentration generally is high-normal or increased in patients who require PN.[36,37] Similarly, Compher et al[23] found plasma-free choline concentration was below normal in 85% of their group of 21 home PN patients. It is interesting to note that although the small amount of choline in lipid emulsion is sufficient to induce a modest increase in the plasma-free choline concentration, which results in a decrease in hepatic aminotransferase abnormalities,[22] it is insufficient to bring plasma-free choline concentrations to normal.[23] These findings were mirrored by Burt et al,[38] Chawla,[14] and Sheard et al.[22,35] Buchman et al[27] and Burt et al[38] found plasma-free choline concentrations decreased to 50% and 33% of normal, respectively, within 1 and 2 weeks, of beginning PN. The phosphatidylcholine contained in the lipid

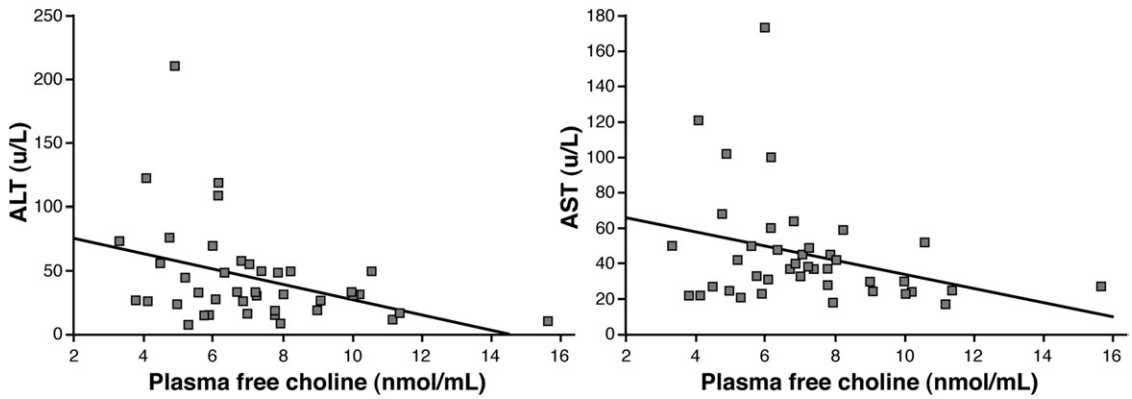

Figure 3. The relationship between plasma-free choline and serum ALT level ($r = -0.34$, $P = .03$) and AST level ($r = -0.37$, $P = .02$). Reprinted with permission from Buchman et al.[34]

emulsion is not converted to choline to any significant degree.[34,39] Much of it is transferred to other lipoproteins or re-enriched with cholesterol to form lipoprotein X.[40] Plasma phosphatidylcholine concentration remains normal during PN.[34]

Those patients who are most dependent on PN are also those who are most likely to develop choline deficiency and hepatic aminotransferase abnormalities.[34] Misra et al[35] found plasma-free choline concentration was reduced significantly in children who required PN when compared with similarly aged control children attending an outpatient surgery clinic. Plasma-free choline concentration decreased within 1 week when human subjects took nothing by mouth and were supported on PN.[27] Hepatic aminotransferase abnormalities were observed within 3 weeks of ingestion of a choline-free diet.[24] Compher et al[23] also described patients with short-bowel syndrome, who no longer require PN, but still have a decreased plasma-free choline concentration despite rigorous attempts to increase their choline via intake of large quantities of choline-rich foods. These foods produce a modest increase in plasma-free choline concentration. These investigators suggested dietary choline malabsorption appeared to continue long after postenterectomy adaptation had taken place and other nutrient absorption was sufficient to avoid PN. Further, Compher et al[23] suggested that bacterial overgrowth, possibly present in some patients with short-bowel syndrome, could result in bacterial degradation of choline to betaine and trimethylamines. Buchman et al[25,27,28] have shown that parenteral choline supplementation reverses hepatic steatosis and hepatic amino transaminase abnormalities associated with short-bowel syndrome/PN-associated liver disease (Figure 4).

Given that choline is the rate-limiting step in acetylcholine synthesis,[41] and acetylcholine is the most significant neurotransmitter in cholinergic cells,[42] it comes as no surprise that choline might play an important role in memory. Choline is transported across the blood-brain barrier in proportion to its plasma concentration.[43] Administration of intravenous choline leads to a rapid increase in brain acetylcholine in rats.[44] Buchman et al[33] described memory abnormalities (delayed visual recall, verbal learning, and visual scanning ability/psychomotor speed) in a small group of choline-deficient home PN patients that improved with choline-supplemented PN when compared with placebo responses. Two case reports that described children with developmental delays, reported memory improvements and improvements on the Denver Developmental Screening Test after oral choline supplementation, with regression when choline supplementation was withdrawn.[45]

Although in long-term PN patients a PN-associated nephropathy has been described,[34,46,47] no specific relationship has yet been identified between choline deficiency and PN nephropathy. In animal models of choline deficiency, however, hemorrhagic nephritis, decreased glomerular filtration rate, and abnormal concentrating ability all have been described as manifestations of choline deficiency.[48]

Clinical Manifestations of Choline Toxicity

The upper limit for choline intake is 3.5 g/day in adults. This is the lowest level at which an adverse effect has been seen in human beings in which it induced hypotension. Shapira et al[49] administered 6 g of oral choline to PN-dependent patients without consequence, presumably because of their malabsorption. This dose together with correction of overall malnutrition led to normalization of the plasma-free choline concentration in 2 patients. Shronts[50] constructed patient diets, and found diets high in choline content (>2 g/day) commonly are consumed by individuals in the United States on a daily basis. Buchman et al,[26] in a dose-escalation study, observed mild nausea, headache, and perspiration in a subject whose plasma-free choline concentration was greater than 200 nmol/mL. (Normal plasma-free choline concentration is 10–15 nmol/mL.)

Modification for Cirrhosis, Renal Failure, Trauma, Sepsis, and Burns

Chawla et al[19] found that the plasma-free choline concentration was decreased significantly to 9.5 ± 0.6

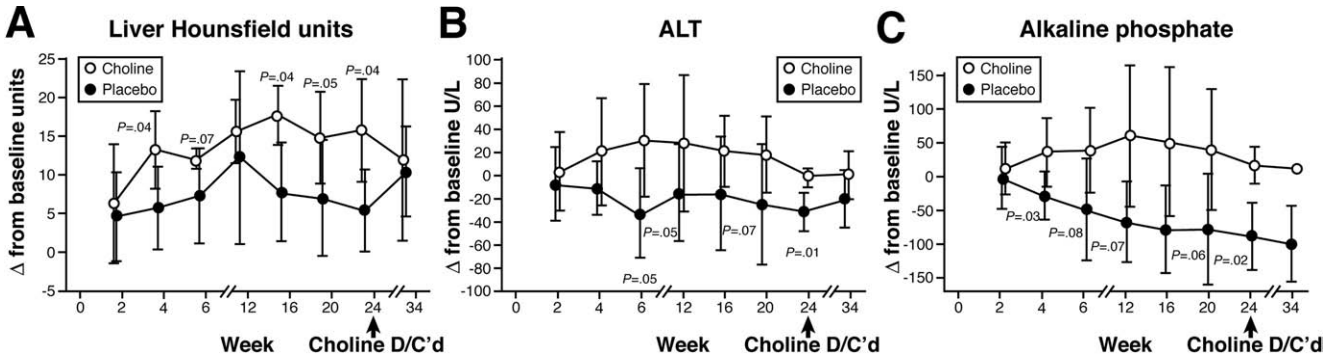

Figure 4. The effect of parenteral choline supplementation on hepatic steatosis in choline-deficient intestinal failure patients who required PN. (*A*) Liver Hounsfield units; (*B*) serum ALT; and (*C*) serum alkaline phosphatase. Reprinted with permission from Buchman et al.[28]

nmol/mL ($P = .05$ vs normal controls) in a group of 8 undernourished hospitalized patients with a variety of medical disorders who ate standard hospital meals. Plasma-free choline concentrations were even lower in a group of undernourished cirrhotic patients who ate the regular hospital meals (7.1 ± 0.9 nmol/mL; n = 9; $P = .001$ vs normal controls), and the lowest of all was in those patients with cirrhosis who were PN-dependent (n = 6; 2.7 ± 0.9 nmol/mL; $P = .001$ vs normal controls). Because of decreased hepatic choline stores in cirrhosis and hepatic failure, the choline requirement may be increased in these patients.

Methotrexate, an inhibitor of the enzyme dihydrofolate reductase, results in decreased availability of folate as a methyl donor, and is associated with the development of hepatic steatosis, and, in later stages, fibrosis. Choline supplementation reverses the methotrexate-induced steatosis in rats.[51,52] There are currently no available human data.

In rodent models, chronic ingestion of a choline-deficient diet leads to development of hepatocellular carcinoma. This is the only nutrient deficiency currently known that in the absence of any known carcinogen leads to development of a malignancy.[6,53]

Not only is there net uptake of choline by the liver, but the kidneys accumulate choline as well.[54] Plasma-free choline concentration is increased significantly (by about 100%) in patients with renal failure, which may represent reduced renal clearance of choline. Free choline substantially is removed by hemodialysis and peritoneal dialysis.[55,56] Renal transplantation leads to a rapid decline in plasma-free choline concentration to normal ranges within 24 hours of transplantation.[57] Correspondingly, kidney donors experienced significant increases in plasma-free choline concentration, which normalized within 3 days.

There are no data on the use of intravenous choline supplementation in patients with cirrhosis or renal failure.

Studies in rodents and canine models have indicated that mortality from endotoxin-induced shock is significantly greater,[58] and hepatic injury is more significant,[59] in rats fed a choline-deficient diet. Endotoxin lead to a reduction in serum-free choline concentrations in a canine model.[60] These investigators hypothesized that this reduction may have been mediated by increased endogenous glucocorticoid steroid release,[61–63] although there was no relationship between increases in cortisol and choline status in mice, guinea pig, or rabbit models.[64] Rivera et al[65] showed that mortality can be decreased and hepatic injury somewhat prevented by provision of a choline-rich diet. Intravenous choline had a similar effect in a canine model.[60] There are currently no available human data.

Serum-free choline concentration has been reported to decrease in human beings by approximately 20%–60% after elective abdominal surgery, total abdominal hysterectomy, brain tumor resection, childbirth (vaginal or caesarian section), and traumatic head injury.[63,66]

Modification for Sex and the Elderly

Some studies have found female rats are less sensitive to choline deficiency than their male counterparts,[67] perhaps because, as shown in mice, the females synthesize a greater degree of their choline requirement via the phosphatidylethanolamine N-methyltransferase pathway.[68] This represents the only source of choline other than from dietary intake. Other studies in rodents have found that choline-deficient males are more susceptible to development of early hepatic steatosis than females.[69] Clinically in human beings, however, plasma-free choline concentration appears to be lower in females than in males,[35] and females appear to be at greater risk for PN-associated hepatic abnormalities.[35]

Kohlmeier et al[70] recently described a genetic polymorphism of the 5,10-methylenetetrahydrofolate dehydrogenase-1958A gene allele (MTHFD1 G1958A) in premenopausal women that provided for a 15-fold higher risk of choline deficiency with end-organ damage (development of hepatic steatosis and/or increased creatine phosphokinase during ingestion of a choline-deficient diet). These investigators hypothesized that this particular single nucleotide polymorphism restricts methyl group availability for endogenous choline synthesis via the phosphatidylethanolamine methyltransferase pathway, and thus becomes the rate-limiting step. Another single nucleotide polymorphism (rs12325817) of the phosphatidylethanolamine transferase gene, which results in decreased or absent endogenous choline synthesis, has been associated with an increased risk for breast cancer development in women.[71] It has been proposed that single nucleotide polymorphism blocks the response of estrogen to the promoter region of phosphatidylethanolamine N-methyltransferase.[72]

There are no data to suggest choline requirements differ in the elderly from that of younger adults.

Relevance to Pregnancy, Lactation, and the Pediatric Population

Choline is transported across the placenta against a concentration gradient[73] and because of that newborns have significantly higher plasma-free choline concentrations than adults.[35,39,74–76] This level decreases rapidly during the first 7 days of life, and then more gradually over the first year toward the normal adult concentration.[35,74–76] The increased plasma-free choline concentration may reflect an increased requirement for choline during early developmental stages, particularly of the brain.[77,78] Therefore, it may be important to maintain an increased plasma-free choline concentration perinatally. Plasma-free choline concentration in the newborn is re-

lated directly to maternal plasma-free choline concentration,[74,76] and is lower in infants requiring PN compared with breast- or formula-fed infants.[39,74,79] Decreased fetal choline availability has been associated with neural tube defects in both rats and human beings.[80,81] In a population-based study of 704 subjects, increased maternal choline intake was associated with a 30% decreased risk for cleft palate in newborns.[82] In rat models, dietary choline supplementation during gestation was associated with enhanced pup performance of both work and reference memory in a maze test.[83]

Choline is secreted in breast milk.[79] The reason for the eventual decrease in plasma-free choline concentration after birth is unknown, but it may be related to the significant choline requirements for phospholipid synthesis in the central nervous system, kidneys, liver, lung, and skeletal muscle.[78]

Summary Recommendations

Research Priorities

Research priorities are as follows: (1) a randomized, multicenter, clinical trial of choline treatment of PN-associated liver disease in adults; (2) determination of normal blood or plasma concentrations of choline in normal infants and toddlers, finding the optimal dose for supplementation, and then a clinical trial of choline supplementation to treat PN-associated liver disease in children; (3) determination of the mechanism for the transport of choline in and out of the red blood cell, and factors that influence this transport mechanism; (4) evaluation of choline-supplemented PN to prevent liver disease; (5) evaluation of choline-supplemented PN to prevent catheter thrombosis and hyperhomocysteinemia; (6) evaluation of choline deficiency as a potential contributor to PN-associated nephropathy; and (7) determination of the optimal dose for intravenous choline supplementation in patients with cirrhosis or renal failure.

Clinical Recommendations

There are no clinical recommendations because choline as an injection is not currently available commercially for use in patients. However, available experimental data suggest an appropriate intake in adults would be 1–2 g of choline chloride daily. No data are available for young children and infants.

Question and Answer Session

DR HOWARD: So the question really is do we need choline in the parenteral patients, and I think it's evident now that there isn't a commercial product so it would have to start with developing one; where do we stand on that now?

DR BUCHMAN: One of the things that we have to think about is that the FDA may be able to assist with product development. In fact, we received funding for much of our research under the Orphan Drug Act, but even the development incentives offered under this law may be insufficient to encourage development of inexpensive products for such a small market. Multicenter clinical trials are very difficult and very expensive undertakings. Fortunately, the NIH has a new mechanism through the U funding for multicenter clinical trials but again money is in short supply.

DR HARDY: Alan, I presume choline or phosphatidylcholine is present in the lipid emulsions from the lecithin that's used to emulsify them. Is there any evidence that choline status can be improved using these solutions?

DR BUCHMAN: Well, as I mentioned, Nancy Sheard showed some 20 years ago that patients who received low-lipid-containing parenteral nutrition had significantly lower concentrations of plasma-free choline than those that received lipid daily, but plasma-free choline concentrations still remained well below normal. For some reason the phosphatidylcholine in the lipid emulsion cannot be utilized. There is only a very small amount of free choline in the lipid emulsions.

DR BORUM: You mentioned that there's interaction among nutrients such as the methyl donors and products of the hepatic transsulfuration pathway, etc, and as you know carnitine and choline have been linked together. Can additional intake of one related nutrient compensate for deficient intake of another?

DR BUCHMAN: That is an excellent point. We need to consider nutrients in the context of similar nutrients, for example, choline with folate and vitamin B_{12}. However, this is a difficult task as it is not currently possible to determine the relative roles of these nutrients, and to what degree additional supplementation of one nutrient can overcome some of the symptoms of deficiency of another. For example, hepatic steatosis exists in PN patients and is treated successfully with choline supplementation despite adequate or more than adequate B_{12} and folate. However, there are probably processes where B_{12} and/or folate can compensate for choline deficiency.

DR SHIKE: If we go beyond abnormal hepatic aminotransferases to the group with more significant severe liver disease or hepatic failure, do you think that choline plays a role in these patients as a single nutrient deficiency, or is it a contributing factor when there are other reasons for liver failure such as viral hepatitis or other unknown causes?

DR BUCHMAN: Well, in the longer-term PN patients, approximately 85% of these patients will have plasma-free choline concentrations that are below normal. The choline they get comes from their diet, so those patients that are most PN-dependent obviously have the lowest choline concentrations. Choline deficiency may be a required step in the development of more severe liver disease, but not sufficient in and of itself. For example, a second "hit"

such as hyperhomocysteinemia, the presence of tumor necrosis factor (TNF), or lipid peroxidation may be necessary to induce progression to more severe liver disease. It may represent a diet-environmental interaction.

DR SHIKE: Specifically those who go into liver failure. Can you tell that they are more choline deficient or there is more functional deficiency related to choline?

DR BUCHMAN: We don't know. Patients with cirrhosis presumably have decreased storage capacity for choline and studies have shown they have very low plasma-free choline concentrations. However, liver failure patients have not been investigated. Usually by the time hepatic failure arrives, the ballgame is over and one often proceeds to transplant.

DR SHULMAN: The data relating choline and steatosis are quite compelling, but how do patients make the jump from simple steatosis to more severe cholestasis, especially in the preterm infant where cholestasis is more predominant? Would you expect any response from choline supplementation?

DR BUCHMAN: First, recent data from our group has shown that choline deficiency does develop in the neonate, but there have been no choline supplementation studies in this patient group yet. The question comes down to whether PN-associated liver disease has the same pathogenesis in the neonate as in the adult, but neonates are more severely affected perhaps because of increased choline requirements and perhaps because prematurity effects the hepatic transsulfuration pathway. Possibly the liver disease that develops in the neonate is largely related to a different process. We just don't yet know the answer. A study of choline supplementation needs to be undertaken. The big question is whether, given an increased choline requirement for growth, should the dose of choline for neonates be based on energy needs or weight, or the amount of choline and its active metabolites in breast milk.

DR JEEJEEBHOY: In order to prove the essentialness of a nutrient, you have to prove it via Cox's postulates. If you have a deficiency you need an identifiable syndrome. If you feed the particular nutrient, it gets better. Sometimes, a nutrient might be conditionally required. For example, cysteine may be conditionally required in liver disease where it is used perhaps not with just "replacement" in mind, but as a pharmacologic agent in larger doses. Where does choline fit in this context?

DR BUCHMAN: If we go back to Stephen Zeisel's study, in 1992, some normal volunteers developed liver abnormalities when placed on a choline-deficient diet; these resolved when a choline-sufficient diet was provided. Similarly in our studies, one subject had hepatic steatosis, which resolved with choline supplementation only to recur 4–10 weeks after choline-supplemented PN was discontinued. We did use a dose that is 200% of the AI, although certainly one that can be easily attained from a normal diet according to data published by Eva Shronts. Plasma-free choline concentrations in some patients were slightly above normal, but well within a nontoxic range. We don't know the minimal dose of choline required, but it may indeed be closer to the AI. The AI, however, is for choline, not a choline salt. As such, 2 g choline chloride, for example, is roughly equivalent to 1.1 g of choline. Perhaps a 2-g dose is necessary for treatment over a 2- to 4-week period, and a 1-g dose for a routine daily intake; we don't have that data.

DR HOWARD: There's been some recent reports of reversing PN cholestasis, especially in children using omega-3 fatty acid solutions. Do you see any connection metabolically between choline's role and omega-3 fat?

DR BUCHMAN: The dietary sources are somewhat similar, but only because choline is ubiquitous in the diet. It is present in greatest concentration in eggs and organ meats, foods which often are discouraged these days. In so far as fish oil emulsions go, I think we need better data. There are only a few case reports in the literature and no placebo-controlled data. In one case report, the child's liver tests worsened following the parenteral fish oil for some time. Fish oils may be anti-inflammatory, although some studies suggest they may be immunostimulatory. Whether or not they might have a role with choline to prevent development of steatohepatitis is unknown.

DR HARDY: Quaternary ammonium compounds are often quite unstable, I wonder if you have any data that would enable the product to be mixed with complete PN mixtures or would it have to be infused separately?

DR BUCHMAN: We have found the choline concentration in choline chloride vials remains stable after at least 5 years. We have also found that recovery of choline from choline chloride ranged between 98% and 102% at 30 days in 3:1 solutions. We have similar data for stability at 7 days in 2:1 solutions; we did not evaluate longer periods.

DR HOWARD: Dr. Buchman, would you like to just briefly mention the research priorities you had outlined?

DR BUCHMAN: I think we need more information on what's the most appropriate dose, what's the minimum dose that we need for both treatment of liver disease and prevention of liver disease. Are there other doses that are required for preventing catheter thrombosis, lowering the homocysteine concentration, or perhaps other aspects such as improving memory in patients? We need to understand whether choline deficiency either is the cause, or contributes to complications that patients develop on parenteral nutrition. We need to develop a commercially available parenteral supplement.

DR COMPHER: Both adult multivitamin preparations in the US had a 50% increase in the content of folate, and when we increase folate we always worry about masking a B_{12} deficiency, can you project whether that would have any impact on choline status?

DR BUCHMAN: Does extra folate mitigate any of the effects of choline deficiency? I would guess that probably it could to some degree but not completely. We were already giving more folate than the AI if one accounts for the fact that intravenously infused folate is 100% bioavailable. We probably also provide more B_{12} than is necessary. We measured B_{12} concentrations on patients on long-term parenteral nutrition; they're all elevated.

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Reprint requests

Address requests for reprints to: Alan L. Buchman, MD, MSPH, Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, 676 N. St. Clair Street, Suite 1400, Chicago, Illinois 60611. e-mail: a-buchman@northwestern.edu; fax: (312) 695-3999.

Conflicts of interest

The author discloses the following: Dr Buchman shares in the intellectual property rights to intravenous choline licensed to Bioniche Pharma USA. The author declares no other relationship with Bioniche Pharma.

STUDIES ON THE EFFECT OF INTRAVENOUSLY ADMINISTERED CHOLINE CHLORIDE IN PATIENTS WITH AND WITHOUT LIVER DISEASE

F. Steigmann, M.D., R. Firestein, M.D., and J. de la Huerga, M.D.

From the Hektoen Institute for Medical Research and the Departments of Internal Medicine and Therapeutics of the Cook County Hospital and the Department of Internal Medicine, University of Illinois College of Medicine, Chicago, Illinois

While acetylcholine, the acetyl derivative of choline, has become well known since the work of Loewi, Dale and others, choline, itself, has not been given much attention until recently.

Choline acts similarly to acetylcholine although to a much lesser degree, the latter being about 1000 times as powerful. Choline, like acetylcholine, imitates closely the effects of parasympathetic stimulation, causing cardiac inhibition, excitation of smooth musculature of the gastro-intestinal tract and bladder wall and secretion of saliva, tears, and sweat. It causes vasodilation and fall in blood pressure. Choline ester is rapidly inactivated by the enzyme cholinesterase which is found in blood and other body tissues. Physostigmine inhibits the action of cholinesterase.

In the past two decades, choline has been shown to be an essential dietary factor, exerting, among other things, profound effect on the storage and transport of fat in the animal.

Diets low in choline ultimately lead to cirrhosis: in the rat the latter can be prevented by the addition of choline alone or in combination with methionine or cystine in small doses[1]. Some investigators were unable to prevent cirrhosis in their animals but found that 10–20 mg. of choline reduced the incidence and severity of liver injury. Choline chloride in doses of 1–6 gms. daily and a diet low in animal fat and cholesterol proved of value in the treatment of patients with cirrhosis of the liver[2]. It was also shown that feeding of choline would reduce the percentage of fat in the liver from approximately 15 to 3 per cent[3]; that choline would prevent or decrease fat deposition after high cholesterol feeding[4]; that it would decrease fat deposition in the liver of patients with diabetes, and that choline would minimize fat deposition in the liver after phosphorus[5] or carbon tetrachloride poisoning[6] and during starvation[7].

The mechanism of the lipotropic effect of choline is, at present, still controversial. Some believe that the lipotropic effect of choline may be due to accelerated phospholipid metabolism; the increase in phospholipid turnover being responsible for ridding the liver of fat[8]. Others believe that choline is necessary in the diet so as to keep an equilibrium between fat in the liver and

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body depots. To date, apparently no evidence has been found that choline increases the rate of oxidation of fat[9].

Since choline has little, if any, effect in preventing accumulation of cholesterol esters, any value choline may have in "cholesterol" fatty livers would appear to be due to improved liver function resulting from removal of neutral fat deposits. In confirmation of this, a number of clinical reports have appeared indicating the successful use of choline in patients with cirrhosis (deficiency type) of liver[2, 10].

The toxicity of choline varies with the route of administration and with the animal. In cats choline 15–20 mg/kg. intravenously was without effect, but 36–65 mg/kg. was a lethal dose. Subcutaneously, much larger doses (200 mg/kg.) could be given to the cat and even larger ones 1 gm. to the rabbit. In man, the doses of choline used varied from 1–9 gm. per day. It was usually given orally in divided doses without any apparent untoward effect. Although there exists the possible danger of sudden flooding of the circulation with choline and consequent depression of heart and blood pressure, such occurrences are very rare. Nevertheless, because of the very marked pharmacologic effects of acetylcholine, choline, too, has been regarded with fear until recent years. Even then, it was still used with trepidation because of some observations that it not only may cause temporary changes in the blood pressure but also more prolonged changes in the morphologic blood picture leading to a hyperchromic type of anemia. Its use in man other than orally, was even more frowned upon[11].

Since many patients with cirrhosis of the liver may present themselves in stuporous or comatose states and hence, cannot be given orally food or medication, the occasional need for intravenous administration of choline is apparent.

To date, few reports have appeared describing the use of the intravenous route for choline administration and any possible side effects from it. In the few reports that have appeared, only few side effects were described. Thus, Watson and Castle[12] gave choline chloride intravenously in a dose of 17 mg/kg. of body weight daily for 30 days in five per cent aqueous solution without intensifying the anemia of a cirrhotic patient. If anything, the values of hemoglobin and red blood cells increased. Cartwright and Wintrobe[13] gave choline chloride intravenously to a patient without observing any untoward effect in the hematologic picture, no anemia or macrocytosis. Barclay and Cooke[14] treated successfully a patient with severe hepato-renal failure by the intravenous administration of 24 gm. of choline during several days. They noted that choline in doses of 2–8 gm. per day intravenously in dextrose and saline caused sweating, at times severe, increased bronchial secretion and painful abdominal cramps. Hence, they concluded that it was dangerous to

give it to severely ill patients. They used atropine 1/75 gr. routinely for prevention of pulmonary edema but the skin continued to be moister than usually. A diffuse, slightly irritating macular rash over the trunk, arms and thighs disappeared after cessation of treatment. Moosnick, et al[15], similarly noted no bad effects in a case of pernicious anemia following intravenous choline therapy. Our group gave choline alone and choline mixed with other lipotropic substances to a number of patients with and without liver disease and noted no untoward symptoms[16, 17].

In this report, we wish to describe detailed observations on a small group of patients who received intravenous choline.

MATERIAL AND METHOD

Twelve patients (nine hospital controls* and three liver cases) were selected for this study. After a fast of 14 hours, the patients had blood drawn for chemical determination, had a complete blood count and an EKG of 12 leads. Blood pressure and pulse were taken and recorded. Phleboclysis of 500 cc. of a five per cent glucose solution in water and containing choline chloride equivalent to 2 gm. choline base was then started. The patient emptied his bladder before the starting of the phleboclysis. The fluid was given at a slow rate for approximately two hours.

Blood pressure and pulse were taken at 15–20 minute intervals. Electrocardiograms were again taken during (after one hour) and at the end of the phleboclysis, when blood chemistry and blood count were also repeated. The urine was collected in two quantities from 0–4 hours and 4–24 hours. The blood was examined for free choline; the urine for choline, albumin and sugar.

During the entire period of the choline phleboclysis, the patients were also observed for any other subjective and objective symptoms such as dizziness, restlessness, palpitation, nausea, vomiting, flushing, sweating, and urticarial eruptions.

RESULTS

No significant changes in the blood pressure or pulse rate were noted during the approximate two hour observation period. In some patients, a slight drop occurred in the blood pressure and pulse rate. This was, however, of only short duration and in most cases, the approximate starting values were reached before the end of the experiment (Table 1).

The electrocardiograms taken during and after the intravenous choline administration showed little change from those taken before the start of the experiment (Graph 1). Only one case showed definite EKG changes in the form of an increase in the P-R interval from 0.18 to 0.3 seconds (Graph 2).

* Hospital controls were patients who suffered from diseases or other organs than the liver and diseases which did not apparently affect the liver.

TABLE 1

Blood pressure and pulse rates (taken every 15 or 20 minutes) of patients receiving phleboclysis of 2 gm. of choline base in 500 cc. of 5% glucose in water

NAME	BEFORE		AFTER PHLEBOCLYSIS											
	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.
C. C.	140/82	64	142/84	64	150/84	64	120/78	66	150/78	72	142/88	64	134/84	64
F. W.	118/78	72	108/78	72	110/78	76	108/70	80	120/78	78	124/80	80	120/84	88
J. T.	150/92	72	150/90	80	150/82	74	144/88	78	160/94	70	152/84	68	162/82	68
H. L.	92/60	68	94/62	78	—	—	—	—	—	—	—	—	—	—
J. P.	118/78	68	114/72	68	110/70	68	110/70	72	108/70	68	110/74	—	108/74	68
E. M.	104/70	100	108/64	96	110/72	96	110/70	100	108/72	100	108/70	100	98/60	80
E. W.	103/72	87	96/76	96	106/72	104	90/70	100	110/80	102	—	—	—	—
W. B.	120/80	76	108/68	78	104/70	80	104/68	76	114/78	80	114/76	—	—	—
A. M.	130/92	68	118/80	62	118/74	84	120/78	84	130/90	88	—	—	—	—
E. W.	114/85	104	114/79	100	114/70	100	115/76	102	108/76	100	108/80	100	103/76	96
S. A.	180/120	66	178/118	60	204/158	68	178/121	68	162/113	72	171/118	68	—	—
E. W.	118/90	80	122/85	76	122/82	80	121/82	80	124/89	80	118/90	80	—	—

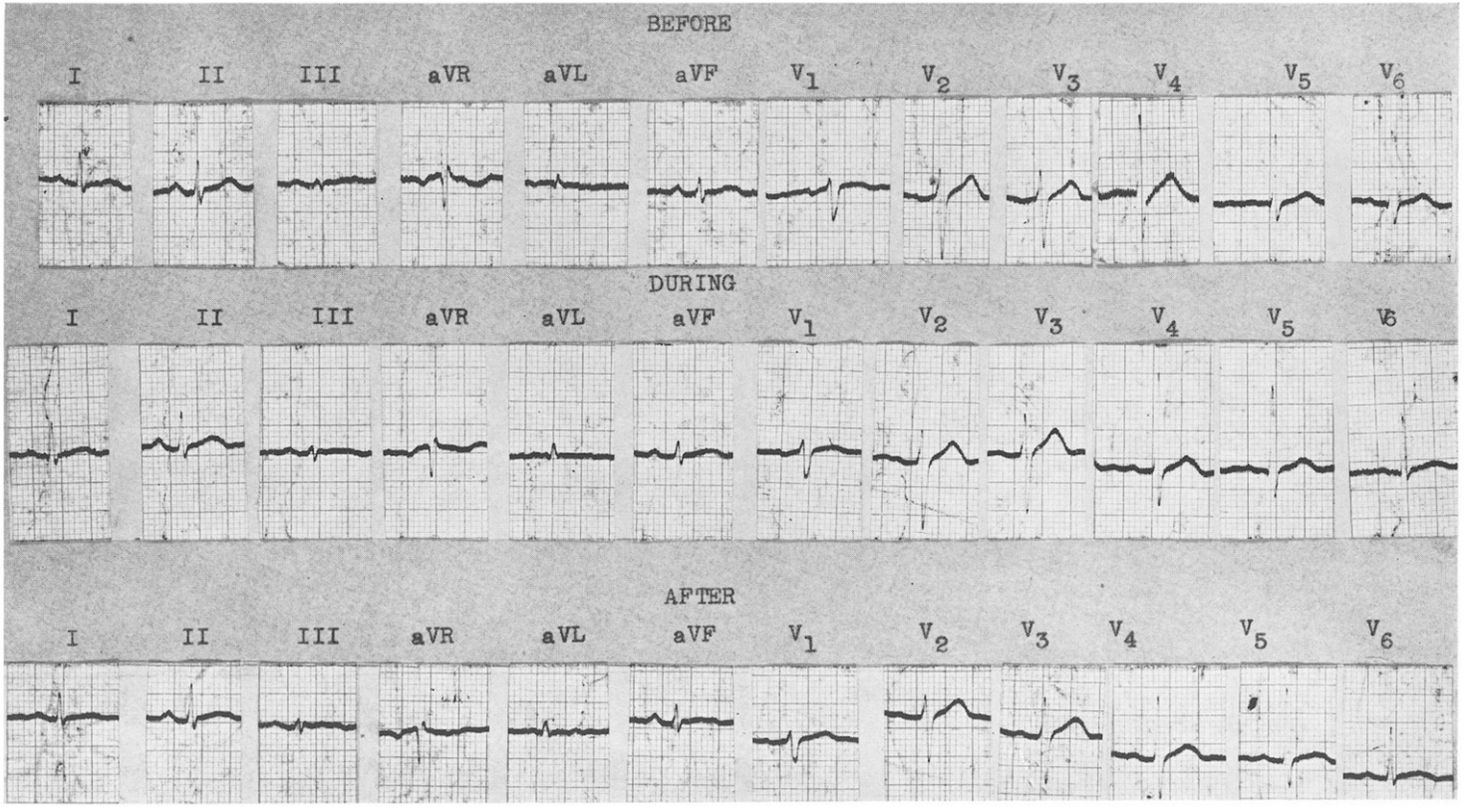

FIG. I. Electrocardiographic leads taken before, during and after intravenous administration of choline chloride showing no apparent changes.

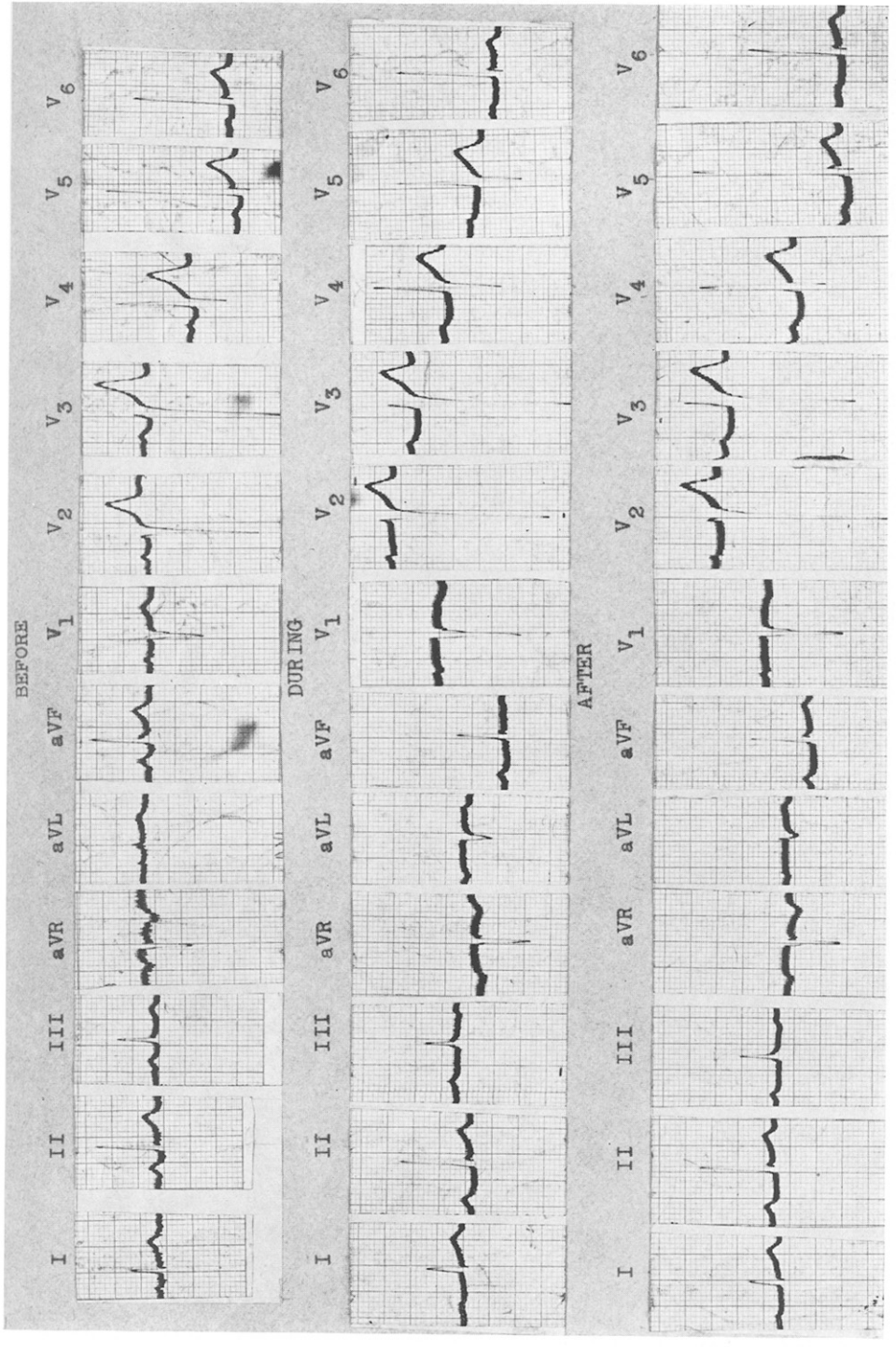

FIG. II. Electrocardiographic leads taken before, during and after intravenous administration of choline chloride showing widening of the P-R interval during and after choline administration. This was the only case which showed electrocardiographic changes.

There were no significant consistent changes in the blood picture following choline phleboclysis. No higher variation than 6 per cent was noted in the hemoglobin determination, some patients having a higher and some a lower percentage. The number of red blood cells was similarly higher in some and lower in others, with 240,000 erythrocytes being the highest variation. In about half of the cases, there was a slight increase of the leucocytes between 1–2000 cells/cubic mm., while in the remainder, the number of white cells remained unchanged. There was a slight increase (up to 7) and a slight decrease (up to 9) of the polymorphonuclear cells in approximately a similar number of patients. In one patient, a large number of band cells (20) appeared following the phleboclysis. In one patient, a slight increase and in two, a slight decrease of

TABLE 2

Urinary excretion of choline in mgms. of choline base after phleboclysis of 2.3 gm. of choline chloride (equivalent to 2 gm. of choline base) in 500 cc. of 5% glucose in water

NAME	URINARY EXCRETION IN MGM. CHOLINE BASE	
	0–4 Hrs.	4–24 Hrs.
E. W.	370.0	4.0
W. B.	285.0	7.3
A. M.	240.0	8.0
A. W.	237.0	6.9
S. A.	198.0	9.2
E. W.	140.0	7.3
J. P.	305.0	12.6
E. M.	220.0	15.6
F. W.	210.0	—
J. T.	225.0	3.5
C. C.	174.0	12.0

the eosinophils was noted. The lymphocytes were slightly depressed in all except one case, while the monocytes increased in four cases.

The urine contained no albumin or sugar in either of the two samples tested. The choline content in the urine determined by the Reineke method described previously[5] was high in the 0–4 hour specimen—up to 370 mg.—and almost negligible in the 4–24 hour specimen, the highest value being 15.6 mg. (Table 2).

In six patients, the plasma concentration of choline was determined by microbiological assay before and after the choline administration. The increase varied from 1.13 to 2.70 mg. per cent with an average of 1.6 mg. per cent (Table 3).

Subjectively, we encountered very few side reactions except in one patient who developed a shaking chill after about 30 minutes. The fluids were im-

mediately discontinued, and he recovered shortly. Of the other eleven patients, some experienced sensations of warmth, slight headache, light headedness and dizziness. Three others had sensations of chilliness. No one had severe sweating, salivation or abdominal discomfort. No nausea, vomiting or urticarial eruptions were noted.

TABLE 3

Plasma concentration (per 100 cc.) of choline in mg. of choline base after phleboclysis of 2.3 gm. of choline chloride (equivalent to 2 gm. of choline base) in 500 cc. of 5% glucose in water

NAME	PLASMA MGM. PER CENT OF CHOLINE BASE	
	Before	After
	Venoclysis	
E. W.	1.94	3.50
W. B.	2.10	4.80
A. M.	3.05	4.30
A. W.	2.23	3.72
S. A.	2.55	4.04
E. W.	2.70	3.83

COMMENTS

The data presented, herewith, would seem to indicate that choline chloride in doses equivalent to 2 gm. choline base can be given intravenously in 5 per cent dextrose by slow drip to patients with and without liver disease, without any serious side effects. The absence of any untoward effects can be postulated as being due to, first the weak pharmacologic choline activity and secondly, to the rather rapid destruction of choline in the body.

CONCLUSION

Our experiences would suggest that choline or mixtures of choline with other lipotropic substances can be given intravenously with impunity in suitable doses whenever indications for such a route exist.

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Tab 3c

FDA Evaluation of Choline Chloride

U.S. FOOD & DRUG ADMINISTRATION

DATE: May 12, 2021

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Suhail Kasim, M.D., M.P.H.
Lead Physician, Pharmacy Compounding Review Team (PCRT)
Office of Specialty Medicine (OSM), Office of New Drugs (OND)

Wafa Harrouk, Ph.D.
Senior Pharmacology/Toxicology Reviewer, Division of Pharm-Tox, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine; PCRT, OSM, OND

Elizabeth Hankla, Pharm.D.
Consumer Safety Officer, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Scientific Advisor (acting), ONDP, OPQ

Daiva Shetty, M.D.
Associate Director, PCRT, OSM, OND

Charles Ganley, M.D.
Director, OSM, OND

Frances Gail Bormel, R.Ph., J.D.
Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Choline Chloride for Inclusion on the 503A Bulk Drug Substances List

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

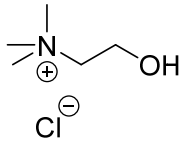
Choline chloride has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It was proposed for use with respect to: liver diseases (including nonalcoholic fatty liver disease) and hepatic steatosis, fetal alcohol spectrum disorder, and atherosclerosis. In addition to these nominated uses, this evaluation considers the use of choline chloride for supplementation in long term total parenteral nutrition.[1] The nomination included information proposing that choline chloride be administered via the parenteral injection route (50 mg/ml as a chloride salt) as slow intravenous and intramuscular preparations.

We have evaluated publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing choline chloride on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[2]

Figure 1: Choline Chloride Structure



[1] Consistent with FDA's practice regarding other bulk drug substances described in the Notice of Proposed Rulemaking entitled "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," published in the *Federal Register* of December 16, 2016 (81 FR 91071, 91075), FDA has opted to evaluate choline chloride for the unnominated use of supplementation in long term total parenteral nutrition. The decision to evaluate this use was informed by an American Society for Parenteral and Enteral Nutrition recommendation that choline be routinely added to adult and pediatric parenteral nutrition (PN) formulations. Many patients requiring parenteral nutrition are suffering from serious conditions. Choline chloride was also nominated for the treatment of mild cognitive impairment. However, FDA did not evaluate this proposed use because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for this use in compounded drug products.

[2] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

Choline chloride is a small molecule found in various animals and plants. This compound is currently marketed as a dietary supplement in capsules, powder, and tablets.

Databases searched for information in preparation of this section included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, and USP/NF.

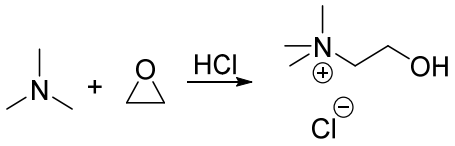
1. Stability of the API and likely dosage forms

No issues concerning the stability of choline chloride have been reported in the literature. Based on its chemical structure, it is likely to be stable under ordinary storage conditions. One study on choline ascorbate, which is an analogue of choline chloride, suggests that the aqueous solution of this compound is very stable at up to 37 °C for one year under ordinary storage conditions (Yillar et al. 2008). Therefore, choline chloride is likely to be stable when compounded as solutions for injection.

2. Probable routes of API synthesis

Current industrial synthesis of choline chloride is shown below in Figure 2. It mainly involves the reaction between trimethylamine and ethylene epoxide in the presence of hydrochloric acid (Zhang 2004; Zeisel 2012).

Figure 2: Choline Chloride Industrial Synthesis



3. Likely impurities[3]

Likely impurities may include:

1) Residual starting materials, like trimethylamine
2) Byproducts such as ethylene glycol

4. Toxicity of those likely impurities

The above-mentioned impurities can be purged thoroughly in the manufacturing process, and are unlikely to be present at a highly toxic level.

[3] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration and chronicity of dosing.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Choline chloride is a white crystalline solid that is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

Choline chloride is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Choline chloride is a small molecule. The nominated compound is easily characterized with various analytical techniques and the preparation of this compound has been well developed. It is likely to be stable under ordinary storage conditions in the proposed dosage form.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Embase, Web of Science, ToxNet, NIH dietary supplement label database, Google, GRAS notice inventory, and Drugs@FDA.

Under FDA's regulations concerning human food, 21 CFR 182.8252 provides that choline chloride is Generally Recognized as Safe (GRAS) when used in accordance with good manufacturing practice.[4] The Environmental Protection Agency (EPA), which regulates choline chloride as an inert ingredient in pesticide products and as a biopesticide,[5] has determined that based on scientific literature from sub-chronic oral toxicity, mutagenicity, and developmental toxicity studies, accidental exposure to choline chloride from food or drinking water in residential settings is non-mutagenic and nontoxic.

[4] See also 21 CFR 582.5252. FDA has considered the GRAS notices concerning choline chloride described herein and their implications insofar as they are relevant in our review of choline chloride's safety or physical and chemical properties as a bulk drug substance in human drug compounding under section 503A. However, these GRAS determinations were made under applicable food safety standards and thus are not dispositive when considering the use of a substance as an active ingredient in a compounded drug product. A substance that is safe when used as a food for ingestion might not be safe as an active ingredient in a drug product, for example, when used for particular patient populations or a route of administration other than oral. Moreover, such GRAS determinations do not indicate that a substance would have any effectiveness for a particular proposed use when used in a compounded human drug product. See 84 FR 4696, 4700.

[5] As a biopesticide, choline chloride is considered a plant growth regulator (PGR) intended for use to increase growth and decrease stress in growing crops. It has a non-toxic mode of action, and as with most PGRs, it is applied at low concentrations because use at high concentrations result in detrimental effects to the plant. (80 FR 78146, 78147).

a. General pharmacology of the drug substance

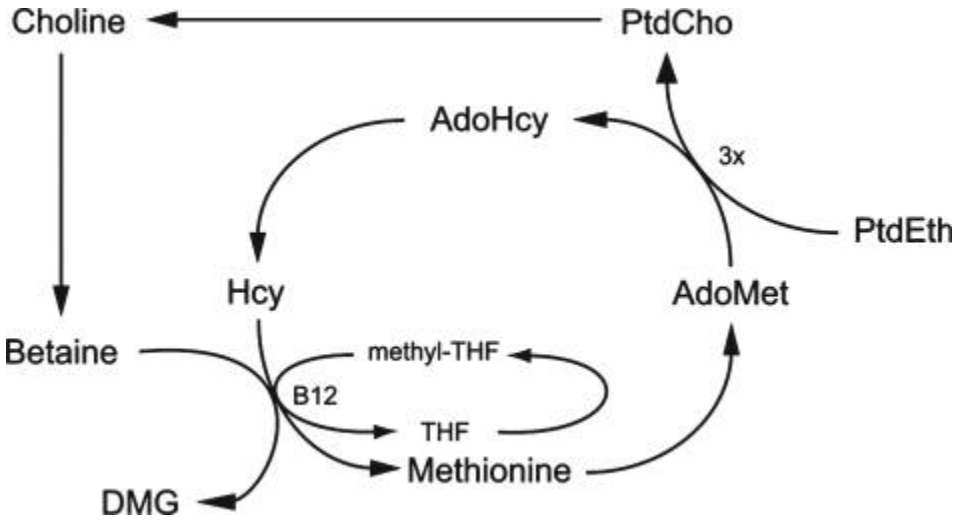
The pharmacology of choline chloride has been reviewed by the Standing Committee on the Scientific Evaluation of Dietary Reference Intake (2000) and the Organization for Economic Cooperation and Development (OECD 2004) for its use as a food and by the Environmental Protection Agency (2015) for its use as an inert ingredient in pesticide products.

Choline chloride is a quaternary ammonium salt consisting of a choline cation and a chloride anion and can readily dissociate into choline and chloride, both of which are present in the human diet and serve many critical functions in the body. According to the National Institutes of Health (NIH) Office of Dietary Supplements (2018), the main dietary sources of choline in the United States consist primarily of animal-based products that are rich in choline such as meat, poultry, fish, dairy products, and eggs. Other sources of choline are the cruciferous vegetables, some beans, nuts, seeds, and whole grains. About half of the dietary choline consumed in the United States is in the form of phosphatidylcholine. Other sources of choline include lecithin (a substance rich in phosphatidylcholine, which is produced during purification of phospholipids). Choline is also found in breast milk and is added to commercial infant formulas. Precise estimates of the percentage of absorption of the different forms of dietary choline in humans are not available (see Appendix 1 for sources of choline).

Choline is an essential nutrient that plays a vital role in the structural integrity of cell membranes, methylation metabolism, cholinergic neurotransmission, transmembrane signaling, lipid and cholesterol transport, and metabolism. The US Institute of Medicine's Food and Nutrition Board established an adequate daily intake of choline: 550 mg for men and 425 mg for women, and an upper daily limit ranging from 3 g/day to 3.5g/day (Food and Nutrition Board, Institute of Medicine 1998; Scientific Committee on Cosmetic Products and Non-Food Products 2003). Choline in the diet is available as free choline or is bound as esters such as phosphocholine, glycerophosphocholine, sphingomyelin, or phosphatidylcholine (Food and Nutrition Board, Institute of Medicine 1998).

Choline exists in many components of the diet (e.g., lecithin in egg yolk, vegetables, and animal fat) and functions as a precursor for acetylcholine, phospholipids, and the methyl donor betaine (see Figure 3). In addition to the dietary supply, choline is formed by *de novo* biosynthesis via an endogenous pathway in the liver via the sequential methylation of phosphatidylethanolamine using S-adenosylmethionine as the methyl donor (Food and Nutrition Board, Institute of Medicine 1998).

Figure 3: Interrelationship of choline, homocysteine, and folate metabolism



Choline is critical during fetal development, particularly during the development of the brain, where it can influence neural tube closure and lifelong memory and learning functions as has been shown in animal models and in humans. Due to these essential needs, the maternal plasma choline serves as the source of choline in the fetus. Breast milk also has high concentrations of choline. This highlights the need for supplemental choline in pregnant and lactating women (Sanders and Zeisel 2007).

Choline requirements differ by sex and stage of life (Zeisel 2006). Men and postmenopausal women are more likely than premenopausal women to develop signs of organ dysfunction on a choline deficient diet. It has been hypothesized that one of the reasons for this is estrogen's ability to enhance de novo synthesis of choline in the liver from phosphatidylcholine. This explains the observation that most premenopausal women and postmenopausal women who are treated with estrogen have a decreased dietary requirement for choline. The other major reason for variation in human dietary requirements for choline is the genetic polymorphism among individuals (Corbin and Zeisel 2012). Among these genetic polymorphism is PEMT (rs12325817) which is present in 40% of women who are nonresponsive to estrogen, and who have the same high choline requirement as men. Other genetic polymorphisms that modify choline requirements by different mechanisms include choline dehydrogenase (CHDH) rs12676 and rs9001, and methylene tetrahydrofolate dehydrogenase 1 (MTHFD1) rs2236225 (Kohlmeier et al., 2005).

Much of the choline metabolism occurs in the liver, and this is among the first organs to accumulate choline absorbed from the intestine. When humans eat diets low in choline, fatty liver is one of the earliest adverse events, and in some people, significant hepatic damage occurs, as assessed by release of hepatic enzymes into blood (Mehedint and Zeisel 2013). Conversely, high blood choline levels have been positively associated with nonalcoholic fatty liver disease (NAFLD), metabolic syndrome (or dyslipidemia), and major adverse cardiovascular events (Imajo et al. 2012). While the principal cause of fatty liver is excessive consumption of alcohol,

the principal causes of NAFLD are obesity, insulin resistance, hyperglycemia, high cholesterol, and elevated triglycerides (Zohrer et al. 2017). Thus, while high blood choline levels have been associated with NAFLD, consuming high levels of choline is not currently listed as a known risk factor for NAFLD.

A very common genetic variation in folate metabolism that has been linked to risk of neural tube defects is an allele, 5,10-methylenetetrahydrofolate dehydrogenase 1958A (MTHFD1). Premenopausal women carrying this polymorphism were found to be 15 times more likely than noncarriers to develop signs of choline deficiency on a low-choline diet (Zeisel 2011). Another gene variation is a single nucleotide polymorphism (SNP) located in the gene encoding for phosphatidylethanolamine N-methyltransferase (PEMT), the enzyme responsible for de novo choline synthesis. More than half of the population has at least 1 allele with this polymorphism, and women with this SNP were 7 times more likely to develop signs of choline deficiency when dietary intake of choline was insufficient (Kohlmeier et al. 2005).

Evaluation of choline as a treatment of atherosclerosis in animals has produced contradictory evidence, as summarized below by Bruger and Oppenheim (1951):

- Steiner (1938) maintained that a diet containing choline with cholesterol appeared to delay but did not prevent the appearance of atherosclerosis in rabbits. Diets enriched in choline alone produced a resolution of aortic lesions previously induced by cholesterol feeding. This was confirmed by other investigators (Morrison and Rossi 1948; Broun et al. 1949). On the other hand, Baumann and Rusch, and Himsworth and Firstbrook were unable to prevent the formation of aortic atheroma by choline feeding in rabbits (Baumann and Rusch 1938; Himsworth H 1938; Firstbrook 1950).
- Bruger and Oppenheim (1951) concluded that the use of choline chloride for the treatment of atherosclerosis and the reputed anti-atherogenic activity of lipotropic factors such as choline have not definitively been established. However, intravenous injections of one gram of phosphatidyl choline (Lipostabil) three times a week into two groups of 5-8 baboons demonstrated reduced atherosclerosis in the group given a hypercholesterolemic diet (Howard et al. 1971).

b. Pharmacokinetics/Toxicokinetics

No in vitro or in vivo animal pharmacokinetic (PK) or toxicokinetic studies were found for choline chloride.

c. Acute toxicity[6]

Animal studies with choline chloride show a low toxicity profile via the oral route of administration. An oral lethal dose (LD_{50})[7] of 3150 – 5000 mg/kg body weight (bw) was seen in rats and 3900-6000 mg/kg in mice (OECD 2004).

When administered via the intraperitoneal route, an LD_{50} of 320 mg/kg bw/day was seen in mice, 450 mg/kg bw/day in rats, and 450 mg/kg bw/day in Guinea pigs (Sahu et al. 1986; Sahu 1989). The clinical signs observed in rats exposed to high doses of choline chloride (5000 mg/kg bw) included restlessness, tachypnea, hypoactivity, convulsions, diarrhea, ruffled coat, staggered gait, and dyspnea. At necropsy, 3 out of 10 rats in the 5000 mg/kg bw group showed inflammation in the lungs. In a separate intraperitoneal study in mice, an LD_{50} of 225 mg/kg was reported.

A powder formulation containing 50% choline chloride, 29% colloidal silicic acid diluted in water (21%) w/v) was injected intraperitoneally into mice (n=5 males and females) at doses ranging between 200 to 1600 mg/kg bw. At the highest doses used, the mice died within 2 minutes (1600 mg/kg bw) to 1 hour (640-800 mg/kg bw) after administration. Delayed mortality (1 day after application) was observed at a dose of 500 mg/kg bw. Symptoms appeared at doses ≥160 mg/kg bw immediately after injection and included tachypnea, convulsions, dyspnea, exophthalmos, and cyanosis. At necropsy, occasional adhesions in the liver were observed (OECD 2004). The serious adverse effects seen in this study may have been attributed to this particular formulation of choline chloride. No data were available for the vehicle control cohorts in this study to make a conclusion regarding the safety of choline chloride when compared to the vehicle control. It is possible that the deaths were due to the formulation that was used in this particular study and not due to choline chloride.

Other acute toxicity studies included an intraperitoneal LD_{50} of 320 mg/kg BW for mice and 450 mg/kg bw for male rats (Sahu et al. 1986; National Institute for Occupational Safety and Health 2014).

In rabbits, topical application of choline chloride (70% aqueous formulation) resulted in very slight irritation (non-classifiable in terms of an irritation scale) of the skin when monitored up to 8 days after topical application (reversibility of irritation was not reported). The same rabbit study reported eye irritation (reddening and tearing) which was seen using the 70% solution for up to 3 hours after application, which was resolved within 1 day of the application (OECD 2004). A summary of the animal acute toxicity studies is shown in Table 1 below.

[6] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[7] LD_{50}, or lethal dose 50, is the dose that results in mortality among 50% of treated animals.

Table 1: Acute Mammalian Toxicology Data for Choline Chloride (40 CFR § 158.2050) [8]

Study/OCSPP Guideline No.	Results
Acute oral toxicity	LD_{50} > 1750 mg/kg (rat) LD_{50} = 3129 mg/kg estimated
Acute intraperitoneal toxicity	LD_{50} = 0.4 g/kg
Acute dermal toxicity	LD_{50} > 5,050 mg/kg (rat)
Acute inhalation toxicity	LC_{50} > 2.03 mg/L (rat)
Primary eye irritation	Minimally irritating (rabbit): minimal irritation observed at one hour post instillation of 70% choline chloride which cleared by 24 hrs
Primary dermal irritation	Nonirritating (rabbit): no irritation was noted at any point throughout the 72-hour study.
Dermal sensitization	Not a sensitizer (guinea pig)

d. Repeat dose toxicity[9]

Mice (n=10/sex/group) were administered choline for 28 days using the following doses/routes of administration:

- 200 mg/kg/day, oral
- 200 mg/kg in 100 µl at every alternate day for 28 days, intraperitoneal
- 200 mg/kg in 50 µl vehicle for every alternate day for 28 days, intranasal
- A concurrent placebo control group, saline (0.9% sodium chloride), was added as a cohort for each route of administration for the same duration of exposure.

No changes were noted in terms of body weight, liver function tests (urea, blood nitrogen, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)), total cholesterol or high density lipoprotein (HDL) levels among choline chloride groups when compared to their respective controls (Mehta et al. 2009).

In another study, male rats (n=24/group) were dosed with either saline (control) or choline chloride at 45, 148.5, or 225 mg/kg/day 5x/week (equivalent to 0.1-0.5 x the LD_{50} of 450 mg/kg/day) via the intraperitoneal route of administration for up to 8 months of dosing (Sahu et al. 1986). Observations were made after 1, 3, and 8 months of treatment. An increase

[8] Table 1 is adapted from the EPA risk assessment for choline chloride; docket # EPA-HQ-OPP-2015-0023.
[9] *Repeated-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

in organ weights was observed in the mid and high dose groups. The organs affected included the lung, kidney, thymus, liver, adrenal glands, peripheral lymph nodes, and spleen at the 3-month necropsy observation.

In the same report, an additional study was conducted with the mid-dose group (10 rats were intraperitoneally injected with 148.5 mg/kg/day, 5x/week) where observations were made after the 3- or 6-month dosing period. At month 3, lymphoid cells were observed around the bronchioles and abnormal lymphatic vessels were seen. Lymph node proliferation was also observed. At the 6-month period, examined lungs showed giant cells in the alveolar lumen along with deposition of collagen and reticulin fibrous formation. While no major changes were seen in the liver at the 3-month observation time point, necrotic changes along with increases in lymphocytic presence were seen in the portal area, and granulomas containing mononuclear cells after the 6-month treatment period (Sahu et al. 1986). No reversibility studies were conducted.

Male guinea pigs dosed intraperitoneally with 50 mg/kg/day choline chloride for 8 weeks showed changes in their lungs including peripheral nodules of small cells, neoplastic bronchiolar epithelium, and carcinoma of the pleural surface of lungs (Sahu 1989).

In summary, under the conditions of the studies reported above, the lung and liver appear to be the main target organs with exposure to high doses of choline chloride. Lung abnormalities were observed in two species (rats and guinea pigs) whereas the liver toxicity was only reported in the rat study, since the guinea pig study did not examine the effect of choline chloride in the liver.

e. Genotoxicity[10]

The genotoxicity potential of choline chloride has been studied by the National Toxicology Program (NTP) because of its use as a dietary supplement in poultry and a lipotropic agent in human drugs (Environmental Protection Agency 2015b; National Toxicology Program 2018). The program included:

- Ames assay: Three separate studies were conducted where strains of Salmonella typhimurium were exposed to choline chloride at up to 10,000 µg/plate with or without metabolic activation. Choline chloride was not considered mutagenic in the conducted assays.
- Sister chromatid exchange (SCE) assay: Two parallel studies were conducted where Chinese hamster ovary (CHO) cells were exposed to choline chloride at concentrations up to 5,000 µg/ml with or without metabolic activation. An increase in SCEs were observed with metabolic activation in one of the studies; however, the increase was sporadic, not dose related and not reproduced in the second parallel study. In a third SCE study with CHO cells exposed to concentrations of choline chloride at up to 5,000 µg/ml, no increase in the number of SCEs was observed.

[10] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

- Chromosome aberration tests: In an in vitro chromosomal aberration assay using (CHO) cells, cells were exposed to choline chloride at up to 5,000 µg/ml with or without metabolic activation. Choline chloride was not considered genotoxic in the assay.

Overall, the available data indicate that choline chloride is not mutagenic/genotoxic under the conditions of the conducted studies.

f. Developmental and reproductive toxicity[11]

Choline is important for fetal and early postnatal development. High levels of choline have been reported in healthy newborns, reflecting an increased requirement for choline during early developmental stages, particularly of the brain (Zeisel 2004).

Decreased fetal choline availability has been associated with neural tube defects in both mice and humans (Fisher et al. 2002; Shaw et al. 2004).

The following information was obtained from the EPA and the OECD risk assessment for choline chloride:

Fertility:
Two groups of male rats were exposed via intraperitoneal administration to 80 mg/kg bw/day choline chloride for either 12 or 24 days. Concurrent intake of choline chloride by feed was estimated to be 10-12 mg/kg BW/day. Compared to the concurrent control groups, there were no differences in body weight gain or in the weights of testes, epididymides, liver, kidney, and adrenals. Treated animals were necropsied at 2, 5, 8 or 12 days after the end of the treatment period and histopathological examination was conducted. Epithelial vacuoles, spermatogonia with pyknotic nuclei and cellular debris were noted 2 days after the end of the treatment. These findings seem to be reversible as normal architecture of the seminiferous tubules was reported 5 days later. Following the full treatment period of 24 days, the damage included various stages of spermatogonia which was seen during the first few days of the study (days 2-8) but was mostly recovered by day 12 of the study (Vachhrajani et al. 1993). No data on fertility effects were reported in females.

Embryofetal toxicity:
A developmental toxicity study was cited by the OECD report on choline chloride where mice were administered dietary doses of choline chloride every other day (equivalent to 1250, 4160, 10800 and 20000 mg/kg/day) from gestation days 1 to 18. Historical control data from 414 pregnant mice served as the control group. Maternal body weight gain was reduced at doses >1250 mg/kg/day. A dose-response increase in fetal loss was observed where all fetuses were

[11] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

resorbed in the highest dose group (20000 mg/kg/day group) followed by a rate of 69% fetal loss in the 10800 mg/kg/day and 35% in the 4160 mg/kg/day dose group. No resorptions occurred in the lowest dose group. A non-statistical increase in fetal malformations was observed where a low incidence of fused ribs was recorded (1 out of 166 fetuses in the low dose group and 1 out of 32 in the 10800 mg/kg/day dose group) and a small increase in the rate of cleft palate was seen in the lowest dose group (1.2%) compared to that seen in the historical controls (1.02%). Under the conditions of the study, the no-observed-adverse-effect-level (NOAEL) for maternal and developmental toxicity was 1250 mg/kg/day (OECD 2004).

Pre/Postnatal toxicity: A study was conducted in rats where pre- and perinatal supplementation of choline was shown to enhance the use of visuospatial memory in two instruments, the 12-arm radial arm maze and a working memory version of the Morris-water maze, whereas perinatal supplementation of betaine (a metabolite of choline) was not associated with a similar pattern of neurobehavior (data taken from a poster where doses were not provided; Williams et al. 2000). Feeding rodents more choline prior to mating increased the rate of brain neurogenesis in the fetus whereas exposure to a low maternal choline diet during the later stages of embryogenesis (days 11–17 of gestation) resulted in a 50% reduction in neural progenitor cell proliferation and twice as much progenitor cell apoptosis in the fetal hippocampus (memory center) compared with fetuses from mothers fed choline-adequate diets. The offspring of choline-deficient dams had diminished visuospatial and auditory memory for the rest of their lives. Conversely, more choline (about 4 times normal dietary levels) fed to pregnant dams enhanced visuospatial and auditory memory in their offspring by as much as 30% throughout life (reviewed in Zeisel 2009).

g. Carcinogenicity[12]

Long term (2-year) carcinogenicity studies have not been conducted for choline chloride. A 72-week feeding study was conducted to investigate the impact of choline chloride (500 mg/kg/day, via the diet) on the liver tumor promoting activity of phenobarbital and 1,1 bis(p-chlorophenyl)-2,2,2-trichloroethane (DTT) in diethylnitrosamine (DEN)-initiated Fischer 344 rats. Animals were observed for an additional period of 30 weeks, during which animals received the same untreated diet as the control group. Necropsy was performed at week 103 and included histopathological assessment of the liver and all organs that developed gross abnormalities. No significant differences were observed between control groups and treated animals with respect to survival rates, body weights, and relative liver weights. There was no increase in the number of neoplastic liver nodules, hepatocellular carcinomas, lung tumors, leukemia or other tumors in choline-treated animals (Shivapurkar et al. 1986). The NOAEL for choline chloride was ≥500 mg/kg/day.

[12] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

Summary:

- Acute toxicity studies showed high threshold of safety (e.g., no toxicity seen at up to 3 g/kg oral exposure in rats studies) using various routes of administration (oral, intraperitoneal, inhalation or topical).
- Repeat dose toxicity studies in rats (148.5 mg/kg/day, 5x/week for 3 or 6 months) resulted in lung abnormalities (lymphoid cells found around bronchioles and abnormal lymphatic vessels at 3 months; giant cells in the alveolar lumen along with fibrosis were seen at 6 months), lymph node proliferation (at 3 months), and liver toxicities (necrosis and increased lymphocytes in the portal area, granulomas with mononuclear cells were observed at 6 months but not at 3 months).
- Choline chloride was not mutagenic/genotoxic as shown in a battery of genotoxicity assays.
- Male rats exposed to 80 mg/kg/day over a period of 24 days showed transient adverse effects on spermatogonia (necrosis) in the first few days of the study; these reversed by day 12 of the study.
- Embryo-fetal studies in mice showed maternal toxicity (decreased maternal bw gain at >1250 mg/kg/day) and fetal mortality (at >1250 mg/kg/day).
- Long term carcinogenicity studies were not conducted for choline chloride. A study assessing the impact of choline chloride on the liver tumor promoting activity of phenobarbital and DTT in DEN-initiated rats did not result in an increased incidence of tumors when compared to controls.
- Exposure to a low maternal choline diet during the later stages of embryogenesis (days 11–17 of gestation) resulted in reduction in neural progenitor cell proliferation, increased cell apoptosis in the fetal hippocampus, compared to fetuses from mothers fed choline-adequate diets. Choline-fed pregnant dams enhanced visuospatial and auditory memory in their offspring.
- Intraperitoneal exposure to choline chloride was conducted in acute toxicity and repeat dose toxicity studies. The lung and liver appear to be the main target organs at mid- and high dose exposure (148.5 and 225 mg/kg/day; equivalent to 24 and 36.45 mg/kg in humans[13]). The reversibility of these findings was not studied. Transient findings of epithelial vacuoles, spermatogonia with pyknotic nuclei and cellular debris were noted among treated males; these findings were reversible in the recovery phase of the study.

Conclusion: Oral exposure to choline chloride is necessary for the normal functioning of the body as has been shown in animal and human studies where a low exposure to toxicity has been reported. Conversely, animal models dosed with choline chloride via the intraperitoneal route of exposure had a NOAEL of only 0.7x and 2x the human equivalent dose (HED) with observed toxicities seen in the lungs, liver and testes.

[13] For the high dose of 225 mg.kg/day, the HED is 36.45 (225 mg/kg/day* 0.162); for the mid dose of 148.5 mg/kg/day, the HED is 24.057 (148.5*0.162).

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), and ClinicalTrials.gov.

a. Reported adverse reactions (FAERS and CAERS)

FAERS

The Office of Surveillance and Epidemiology conducted a search of FAERS for reports of adverse events (AEs) for choline chloride in addition to a review of the medical literature for potential safety signals reported with choline chloride through October 12, 2020. Six cases were identified that reported both exposure to choline chloride and at least one AE.

Two cases involved gastrointestinal AEs (diarrhea and vomiting) after a weight loss injection containing multiple substances including choline chloride was administered. While gastrointestinal conditions such as nausea and vomiting have been reported with choline chloride, especially at high doses, the multiple substances in the weight loss injection are likely to have resulted in these adverse events.

Two cases involved injection site AEs (injection site pain, injection site mass, and injection site hypoesthesia) which can occur with any intramuscular or subcutaneous injection.

One case involved a drug hypersensitivity adverse event after taking choline chloride via an unknown route, in addition to 12 other medications. Insufficient information was provided to make a causal assessment, particularly due to the large number of concomitant medications.

The final case involved increased blood pressure, headache, anxiety, and restlessness after taking "skinny shots" (for weight loss) containing choline, inositol, and methionine, in addition to oral naltrexone/bupropion (Contrave). These AEs are likely related to Contrave, which is labeled for hypertension and neuropsychiatric AEs including anxiety.

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of AEs involving food, cosmetics, and dietary supplements in CAERS. A search of CAERS was conducted for AEs associated with choline chloride on August 24, 2020, based on the term "choline chloride." Six cases were spontaneously reported from July 2013 to June 2018. The age of the persons consuming choline chloride was provided for two cases.

Two cases involved drinking Verve Energy Supplement (Vemma Nutrition Company), which contains more than 20 vitamins, minerals, and other ingredients, including choline chloride and caffeine. It is not possible to determine whether a causal connection exists between the AEs reported in these two cases and choline chloride because of the large number of other substances in the Verve Energy Supplement.

- In the first case, a 21-year-old female reported symptoms were vomiting, nephrolithiasis, and increased body temperature, and the consumer went to the Emergency Room (ER).
- In the second case, the reported symptoms were hypertension and increased heart rate and the consumer went to the ER.

Three cases involved consumers using Clear Muscle Performance products.

- The first case concerned a consumer taking two oral capsules of Clear Muscle (Iovate Heath Sciences USA Inc) containing choline chloride, veggie, silicon dioxide, water, and hypromellose, and later in the same day reported racing heart beat and sweating (coded as cardiac fibrillation, hyperhidrosis, and increased heart rate), which resolved spontaneously. No medical intervention was reported.
- The next case concerned a consumer choking on Clear Muscle Performance Series Liquid Capsules (Iovate Health Sciences International Inc.) containing betator (free acid beta-hydroxy-beta-methylbutyrate, choline chloride, silicon dioxide, water, and hypromellose) and "ending up in a hospital." No additional information was provided.
- The third case concerned a 43-year-old consumer with history of asthma managed on combination inhaler medication containing beclometasone dipropionate/formoterol fumarate dihydrate in addition to albuterol sulfate inhaler treatment who experienced severe asthma exacerbation while using Clear Muscle Performance Series Liquid Capsules containing choline chloride, betator, l-carnitine, and green coffee.

Insufficient information was provided to interpret the contribution of choline chloride in these three cases.

A consumer who was on Irwin Naturals Liquid Collagen, a dietary supplement containing choline (as chloride chloride) among other nutritional supplemental ingredients[14], consumed the product daily for almost a month and half until the consumer began experiencing stomach ache, nausea, and dark blood stool which was increasing in frequency. The consumer was prescribed Omeprazole 20 mg and recommended to follow up if there was no improvement in condition. There is no further information reported. Considering that there are many other substances in the dietary supplement, it is not possible to determine whether a causal connection exists between choline chloride and the adverse events reported.

b. Clinical trials assessing safety

In most clinical studies, choline has been found to be well tolerated and not associated with significant AEs. Adverse events have been reported at higher doses and include the following:

- Mild nausea, headache, and perspiration were observed at plasma-free choline concentrations greater than 200 nmol/ml[15] (Buchman et al. 1994)

[14] This product is sold on Amazon (https://www.amazon.com/Irwin-Naturals-Collagen-Hydrolyzed-Anti-Aging/dp/B081NP1J1V/ref=sr_1_13?dchild=1&keywords=irwin+naturals+liquid+collagen+ascorbic&qid=1614777906&sr=8-13). The following ingredients are listed on the product's label: thiamin (as thiamin hydrochloride), niacin (as niacinamide), Vitamin B6 (as pyridoxine hydrochloride), biotin, choline (as choline chloride), hydrolyzed collagen, antioxidant blend, and horsetail.

[15] Normal free plasma choline concentrations are 10 – 15 nmol/ml.

- Choline in doses much higher than daily intake from food have been associated with fishy body odor, sweating, diarrhea, salivation, and hypotension in humans (Food and Nutrition Board, Institute of Medicine 1998).
- In patients with tardive dyskinesia and cerebellar ataxia, doses of 10 and 16 grams/day (dosage form or route of administration not specified) administered for 2 to 6 weeks, were associated with fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects (Davis et al. 1975).
- Daily oral administration of 10 g choline chloride (7.5 g choline) in a small number of patients with Alzheimer's disease had a slight hypotensive effect, but no other effects were noted (Boyd et al. 1977).
- Hypotension has been observed in adults after choline intake of 3.5 g/day, which is the recommended upper daily limit for adequate daily intake of choline. (Buchman 2009).

c. Pharmacokinetic (PK) data

<u>Single-dose oral human pharmacokinetic (PK) study:</u>
Eight patients with movement disorders were each given a single oral dose of choline chloride, 5 grams, and then observed for at least 24 hours. Peak levels were obtained at four hours after the oral dose and by 24 hours most values had returned to baseline. Mean increase in plasma choline concentration was 11.3 nmol/mL with a range of 4.8 to 19.3 nmol/mL (Figure 4; Hollister et al. 1978).

Figure 4: Plasma Choline Concentrations

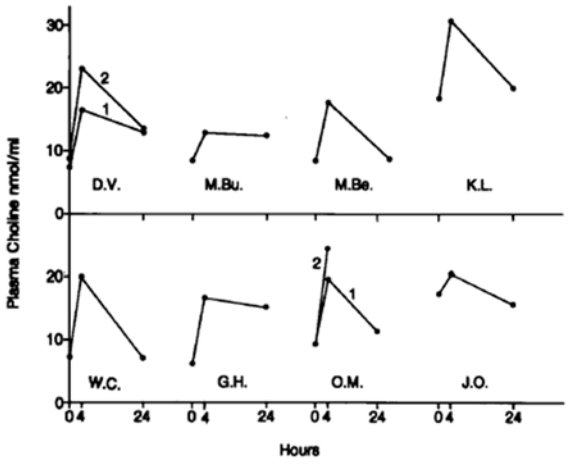


FIG. 1

Changes in plasma choline concentrations following single 5 g dose in 8 patients. Two patients had two trials (1 and 2).

Source: Hollister LE, Jenden DJ, Amaral JR et al. 1978. Plasma concentrations of choline in man following choline chloride. Life Sciences 23:17-22

Multiple-dose oral human PK studies:

- Seven patients with movement disorders were given an initial dose of choline chloride, one gram, four times daily (4 grams total daily dose), increased progressively every three days to 8, 16, and 20-gram daily doses and the 20-gram daily dose was then maintained for 4 weeks. Plasma concentrations of choline increased as the dose was increased; however, dose-dependence was not strong and the slope was shallow. The authors noted that this relatively flat dose-concentration curve was somewhat different from what has been described by others (Growdon et al. 1977; Hollister et al. 1978).

- Choline chloride was administered orally (3 to 15 g per day) to five patients with Huntington's chorea. A long-lasting dose-dependent elevation of the concentration of free choline in plasma was obtained and the highest plasma concentrations (25 to 30 nmol/ml) were of the same magnitude as those that increase brain acetylcholine content in the rat. However, the choline treatment did not conclusively alter the involuntary movements of these patients (Aquilonius and Eckernas 1975; Aquilonius and Eckernas 1977).

Multiple-dose intermittent intravenous human PK study:
Four patients receiving long-term parenteral nutrition received a total of four intermittent 12-hour intravenous infusions of choline chloride on consecutive days with the amount of chloride infused being 7 mmol (1 gram) on Day 1, 14 mmol (2 grams) on Day 2, 28 mmol (4 grams) on Day 3, and 56 mmol (8 grams) on Day 4. Plasma choline concentrations were determined at baseline, ¼, 1, 3, 6, and 12 hours and at 3 and 12 hours after the infusion ended and in 24-hour urine collections.

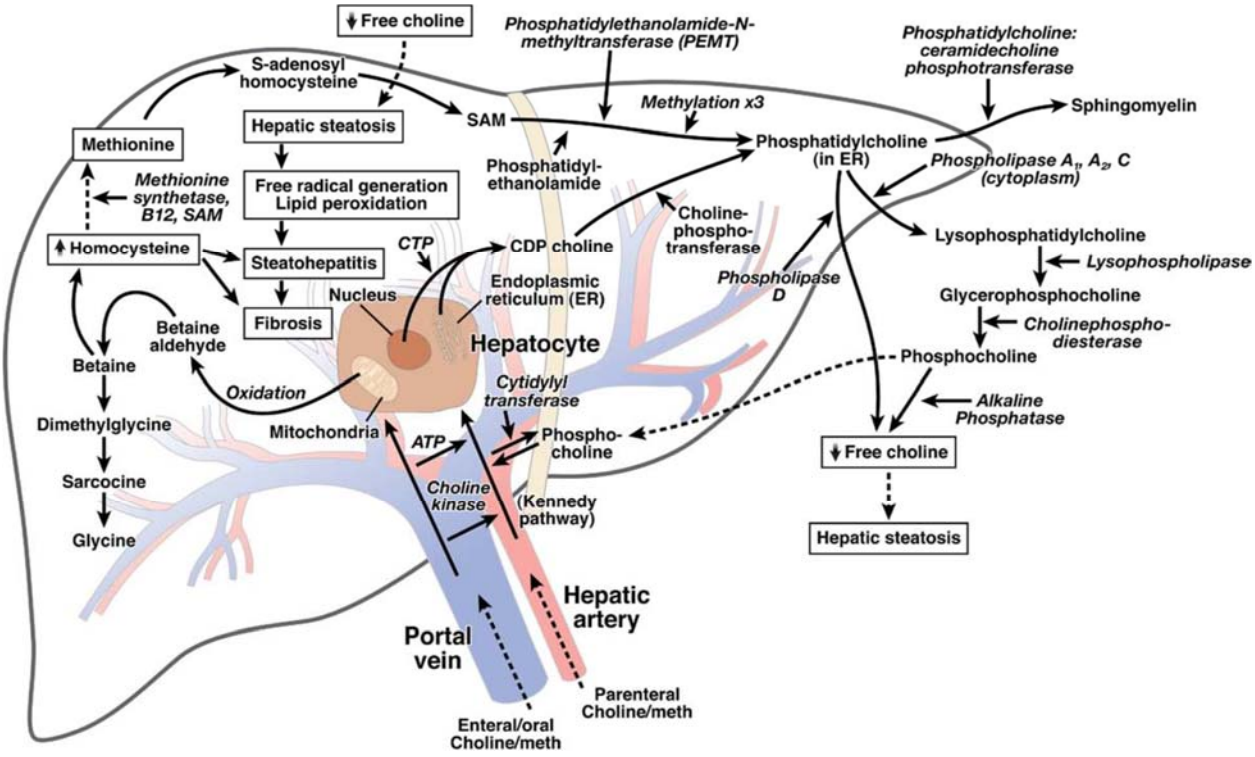
All four subjects had low plasma free choline at baseline (mean ± SD = 5.2 ± 2.1; range 2.7 to 7.2 with normal = 11.4 ± 3.7 nmol /ml); the plasma choline levels increased to normal and supranormal levels during the choline chloride infusion. No side effects were attributable to the choline infusion in 3 of the 4 subjects; however, the fourth subject had mild nausea, headache, and sweating on the 4th day (while receiving 56 mmol or 8 grams) of the choline infusion. The nausea resolved within 2 to 3 hours after the infusion was stopped. The subject's plasma free choline level at the time of symptom development was 230 nmol/ml. No electrocardiographic or respiratory changes were noted.

The authors concluded: a) the elimination of choline is saturable at least at significant infusion rates, and b) plasma levels should be monitored in patients with renal or hepatic insufficiency or both because markedly elevated plasma free choline concentrations may be associated with mild nausea, headache, and sweating (Buchman et al. 1994).

These same four subjects were then prescribed 1 to 4 grams of choline chloride (based upon the previous pharmacokinetic data) to add to their nightly total parenteral nutrition (TPN) solution for 6 weeks. One subject required two downward adjustments in the choline chloride due to "mild nausea" (Buchman et al. 1995).

The many metabolic pathways of choline is illustrated in Figure 5 below (Buchman 2009). The availability of endogenous choline is modified by metabolic methyl-exchange relationships between choline and three nutrients: methionine, folate, and vitamin B_{12}. When choline is ingested, it is absorbed from the lumen of the small intestine. Important metabolites of choline include betaine, phosphocholine, glycerophosphocholine, and lysophosphatidylcholine.

Figure 5: Choline Chloride Metabolic Pathways



Source: Buchman AL. 2009. The addition of choline to parenteral nutrition. Gastroenterology 137: S119-128.

d. Availability of alternative approved therapies that may be as safe or safer

See section II.C.3.

Conclusions: In most clinical studies, choline has been found to be well-tolerated and not associated with significant adverse events. With doses much higher than the daily intake from food, choline has been associated with nausea, fishy body odor, sweating, diarrhea, salivation, and hypotension in humans.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

    a. Treatment of liver diseases[16] (including nonalcoholic fatty liver disease) and use with respect to hepatic steatosis

Hepatic steatosis is not a disease. Hepatic steatosis (or fatty liver) is defined as the presence of large and small vesicles of fat, predominantly triglycerides, accumulating within hepatocytes. Typically, hepatic steatosis is transient and is not seen on an imaging modality unless more than five percent of hepatocytes have triglyceride accumulation. Most humans who have evidence of hepatic steatosis are not affected by its presence; it is a benign finding. In rare instances over many years to several decades, chronic liver disease may develop as a result of chronic inflammation, hepatocyte degeneration, and scarring. This finding is called "steatohepatitis." If liver fibrosis and steatohepatitis progress, there is the possibility that a patient may develop cirrhosis and, in some patients, end-stage liver disease may result (Karanjia et al. 2016). At present, clinicians cannot predict which patients are likely to progress from benign steatosis to steatohepatitis, cirrhosis, or end-stage liver disease. However, most patients who have benign steatosis do not progress to having liver disease, and steatosis is reversible, e.g., by abstaining from alcoholic beverages, weight loss, improved diet, and glucose control in some diabetic patients.

Fatty liver disease is divided into alcohol-related fatty liver disease and NAFLD. The definition of NAFLD requires that (i) there is evidence of hepatic steatosis, either by imaging or by histology and (ii) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders (Chalasani et al. 2012). Thus, NAFLD is a diagnosis of exclusion requiring the presence of hepatic steatosis and the exclusion of other causes of hepatic steatosis (Vos 2017).

NAFLD is a spectrum that ranges from non-alcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), which is an extreme form of NAFLD and is regarded as a major cause of cirrhosis. NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes (Chalasani et al. 2012). NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis (Chalasani et al. 2012).

While the principal cause of fatty liver is excessive consumption of alcohol, the principal causes of NAFLD are obesity, insulin resistance, hyperglycemia, high cholesterol, and elevated

[16] On 01/28/2018, McGuff Compounding Pharmacy Services, Inc (MCPS) submitted information to docket FDA-2015-N-3534 and nominated choline chloride for the proposed use of treating "liver diseases." The scientific article submitted in support of this proposed use was "Studies on the effects of intravenously administered choline chloride with and without liver disease. (Stiegmann F, 1953)." Although the publication described administering intravenous choline alone and choline mixed with other lipotropic substances to a number of patients with and without liver diseases, it appears there may have been only three patients with liver disease. There was no further information characterizing the etiology or stage of the liver disease. The study authors described the weak pharmacological activity of choline; however, the information in the referenced publication is too limited to draw any conclusions on the effectiveness of choline chloride broadly for liver diseases.

triglycerides (Zohrer et al 2017). While high blood choline levels have been associated with NAFLD, high levels of choline are not currently listed as a known risk factor for NAFLD (Oregon State University).

Treatments for NAFLD (Vos et al 2017; European Association for the Study of the Liver, 2016) include:

- Limiting daily alcohol consumption up to 30 grams (men) or 20 grams (women) or stopping alcohol consumption
- Avoid fructose-containing beverages and foods
- Treatment of comorbidities, e.g., obesity (weight management through lifestyle improvements), type 2 diabetes mellitus, dyslipidemia, hypertension, and sleep apnea
- Increasing physical activity
- Considering bariatric surgery in select individuals with NAFLD and other serious comorbidities

It should be noted that humans eating low choline diets can develop liver damage (elevated alanine aminotransferase) and fatty liver (Corbin and Zeisel 2012). The elevated alanine aminotransferase due to low choline diets occurs secondary to hepatocyte apoptosis (Zeisel 2008). The hepatosteatosis due to low choline diets occurs because a lack of phosphatidylcholine limits the export of excess triglyceride from liver in lipoproteins (Zeisel 2008). To treat a low choline diet, the amount of choline in the diet needs to be increased by eating foods high in choline, e.g., dairy, liver, eggs, legumes, nuts, beef, leafy greens, seed oils, and grain germs (Guerrerio et al. 2012).

Humans on long-term parenteral nutrition (PN) that lack adequate choline will show a reversal of hepatic steatosis and a decrease in serum aminotransferases with choline supplementation (Guerrerio et al. 2012). In a paper published on behalf of the European Society for Clinical Nutrition and Metabolism (ESPEN), intestinal failure associated liver disease (IFALD) is a term referring to "liver injury that may occur because of multiple factors relating to chronic intestinal failure, including, but not limited to, parenteral nutrition" (Lal et al. 2018). The authors (Lal et al. 2018) make the following comments:

> "Pharmacological approaches evaluated to treat IFALD include the use of choline, taurine or carnitine; the use of ursodeoxycholic acid and the use of antibiotic therapy for bacterial overgrowth. Based on the evidence available to-date, we cannot currently recommend their routine clinical use in managing IFALD. However, nutritional approaches, aimed at minimizing PN caloric overfeeding and optimizing oral/enteral nutrition should be considered. Thus, methods to optimize enteral absorption and potentially reduce the parenteral calorie load (for example, distal enteral tube feeding) should be instituted…."

Six practice guidelines pertaining to the treatment of NAFLD were identified, of which one practice guideline pertained to this illness in children. Use of choline chloride as a treatment of NAFLD was <u>not</u> mentioned in any of these treatment guidelines (Chalasani et al. 2012; Cotrim et

al. 2016; European Association for the Study of the Liver, 2016; National Institute for Health and Care Excellence 2016; Vos et al. 2017; Chalasani et al. 2018). One practice guideline specifically stated that nutritional supplements do not show scientific data strong enough to support their recommendation as a treatment of NAFLD (Cotrim et al. 2016). The pediatric guideline stated that no currently available medications or supplements were recommended to treat NAFLD because none have been proven to benefit the majority of patient with NAFLD (Vos et al. 2017).

We identified one trial evaluating the effectiveness of choline (Pro DHA Steatolip Plus pills containing algal docosahexaenoic acid (DHA) 250 mg, choline 201 mg, and vitamin E 39 UI) in the treatment of NAFLD (Zohrer et al. 2017). Forty-three children and adolescents (aged 4-16 years; 13 children and 30 adolescents) with baseline liver biopsy confirming NASH were all placed on lifestyle modification for 12 months. The control group received daily placebo pills for the first 6 months of the study, while the active group received daily supplement pills containing DHA, choline, and vitamin E for the first 6 months of the study. All subjects were to undergo liver ultrasound and blood tests at 12 months. Liver biopsies at 12 months were offered only to the subgroup treated with Pro DHA Steatolip Plus pills. Normal liver without steatosis (grade 0) was defined as having normal liver echo-texture; mild steatosis (grade 1) as slight and diffuse increase in fine parenchymal echoes with normal visualization of diaphragm and portal vein borders; moderate steatosis (grade 2) as a moderate and diffuse increase in fine echoes with slightly impaired visualization of diaphragm and portal vein borders; and severe steatosis (grade 3) as fine echoes with poor or no visualization of diaphragm, portal vein borders, and posterior portion of the right lobe.

Forty children completed the trial. See Table 2 below from Zohrer et al. (2017). Each column in the table shows the percentage grade of steatosis at baseline (the columns information is not for the number of subjects or responders) and the percent change in outcome for steatosis based on ultrasound at 12 months. It is possible that mean values were considered in the analysis, although that information is not specified. The primary outcome measure of improvement in liver hyperechogenicity[17] by liver ultrasound at 12 months decreased from 50% to 5% of patients in the active-treated subjects with severe steatosis at baseline. The problem with this subgroup analysis is that there was also a decrease in the placebo group with severe steatosis at baseline. The statistical analysis was a within treatment group comparison of baseline to 1-year and did not compare the treated group to the placebo group.

[17] A single blinded physician evaluated the ultrasound using the following scale: Normal liver without steatosis (grade 0) was defined as having normal liver echo-texture; mild steatosis (grade 1) as slight and diffuse increase in fine parenchymal echoes with normal visualization of diaphragm and portal vein borders; moderate steatosis (grade 2) as a moderate and diffuse increase in fine echoes with slightly impaired visualization of diaphragm and portal vein borders; and severe steatosis (grade 3) as fine echoes with poor or no visualization of diaphragm, portal vein borders, and posterior portion of the right lobe.

Table 2: Liver Steatosis by Ultrasound at Baseline and After 12 Months in Both Treatment Groups

	Placebo			DHA–CHO–VE		
%	Baseline	12 mo	*p*	Baseline	12 mo	*p*
No steatosis	0	0	—	0	35	—
Mild	25	45	0.18	15	35	0.14
Moderate	40	45	0.75	40	25	0.31
Severe	35	15	0.14	50	5	0.001*

Note: DHA–CHO–VE, docosahexaenoic acid, choline, and vitamin E.
*χ^2 test, $p < 0.05$ was considered significant.

Source: Zohrer E, Alisi A, Jahnel J et al. 2017. Efficacy of docosahexaenoic acid-choline-vitamin E in paediatric NASH: a randomized controlled clinical trial. Applied Physiology, Nutrition, And Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme 42:948-954.

The authors also indicated that alanine aminotransferase and fasting glucose improved in the active-treated group. But, as noted in the table below, these changes were similar to placebo. See Table 3 below from Zohrer et al. (2017).

Table 3: Clinical and Laboratory Variables in Placebo and Treatment Groups

	Placebo			Treatment		
	Baseline	12 mo	*p*	Baseline	12 mo	*p*
Sex (male/female)	10/10	10/10	—	14/6	14/6	—
Age (y)	13.2 (2.1)	14.2 (2.1)	0.15	13.2 (2.3)	14.2 (2.3)	0.19
Weight (kg)	66.3 (15.1)	66.4 (15.3)	0.97	68.0 (18.7)	67.3 (14.8)	0.90
BMI (kg/m²)	28.3 (5.3)	28.1 (5.2)	0.90	27.6 (4.0)	27.7 (4.9)	0.71
WC (cm)	89.9 (9.7)	89.1 (9.5)	0.79	86.7 (10.3)	90.9 (10.0)	0.22
AST (UI/L)	33.1 (18.3)	34.6 (36.3)	0.87	36.2 (13.0)	31.2 (15.0)	0.28
ALT (UI/L)	51.2 (51.6)	32.5 (17.8)	0.14	53.5 (32.6)	35.3 (20.7)	**0.04**
Uric acid (mg/dL)	6.5 (3.0)	10.5 (17.4)	0.33	5.3 (0.9)	5.2 (1.0)	0.80
Total cholesterol (mg/dL)	154.5 (30.1)	143.4 (17.9)	0.17	150.1 (31.5)	146.5 (28.4)	0.71
LDL cholesterol (mg/dL)	100.8 (37.6)	94.5 (29.7)	0.57	84.0 (29.4)	76.1 (23.7)	0.37
HDL cholesterol (mg/dL)	46.6 (8.3)	48.6 (8.2)	0.46	47.3 (7.9)	49.65 (11.9)	0.48
Triglycerides (mg/dL)	87.2 (46.2)	81.5 (37.2)	0.68	101.2 (51.3)	82.1 (47.6)	0.24
Glucose (mg/dL)	82.5 (7.2)	80.1 (6.5)	0.27	85.40 (7.5)	81.0 (5.3)	**0.04**
Insulin (mU/L)	22.3 (14.4)	26.2 (21.6)	0.51	21.9 (14.4)	20.7 (12.7)	0.78
HOMA-IR	4.5 (3.0)	5.1 (3.9)	0.64	4.6 (3.1)	4.1 (2.4)	0.53

Note: Except for sex (actual patient numbers), data are shown with mean (±SD). Bold text indicates significant difference ($p < 0.05$). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; WC, waist circumference.

Source: Zohrer E, Alisi A, Jahnel J et al. 2017. Efficacy of docosahexaenoic acid-choline-vitamin E in paediatric NASH: a randomized controlled clinical trial. Applied Physiology, Nutrition, And Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme 42:948-954.

No AEs were reported.

Some additional issues about this study include:

- The authors noted that the results from this study in the active-treated group were like those previously observed with DHA alone.
- The multiple treatments prevent attributing any benefit to the choline.
- No baseline choline blood levels were obtained; thus, it is unknown whether any of the study participants had choline deficiency.
- It was unclear why treatment ended at completion of Month 6 (instead of at completion at Month 12) because the endpoints were not evaluated until Month 12.

In a study of 664 subjects enrolled in a multicenter prospective NASH Clinical Research Network, only one of the four groups (postmenopausal women n=194) demonstrated an association of decreased choline intake with worse liver fibrosis ($p = 0.002$) once factors associated with NAFLD (age, race-ethnicity, obesity, elevated triglycerides, diabetes, alcohol use, and steroid use) were considered in multiple ordinal logistic regression models (Guerrerio et al. 2012). Choline intake was not identified as a contributor to liver disease severity in the three remaining groups of children (n=114), men (n=240), or premenopausal women (n=116).

Regarding use of choline chloride for the treatment of cirrhosis of the liver, a clinical trial reported in 1946 that treatment of 20 patients with 1.5 to 3 grams of "choline" (it is unclear if choline chloride was administered) and the same amount of cystine daily divided into three doses for periods of one to five months (in addition to a high protein and low fat diet and a once daily supplement of 30-45 grams of brewers' yeast) compared to 15 control patients resulted in improvement only in a subgroup of 8 patients in the treatment group with enlarged livers (Beams 1946).

Due to the small number of responding patients, the multiple treatments provided and the confusion regarding whether chlorine chloride was administered, it is not possible to draw any conclusion regarding the efficacy of choline chloride for the treatment of cirrhosis of the liver. A case study was reported in 1947 of a 45-year old female who had undergone 106 paracenteses for cirrhosis and then over several years improved on a high protein diet, supplemented with methionine, liver injections, brewer's yeast tablets, choline chloride 5 grains three times a day, and Vitamin B injections (Burns 1947). The patient was then switched to Choline Di-Hydrogen Citrate by Lilly as her only medication.

Conclusion: Theoretically, patients who were to consume a diet deficient in choline could develop NAFLD; however, since the US diet is rich in choline-containing foods, patients are unlikely to need a change in their diet in order to include choline-rich foods (Oregon State University).[18] We could not find clinical evidence that choline chloride administration will be effective in the treatment of NAFLD that is not related to a deficiency of choline.

[18] The primary type of choline in the diet is in the form of phosphatidylcholine; foods rich in choline include eggs, meat, poultry, fish, cruciferous vegetables (cabbage family), peanuts, and dairy products.

Hepatic steatosis is not specific to a disease condition. There was insufficient information to evaluate the proposed use of choline chloride with respect to hepatic steatosis. The supporting scientific literature submitted by the nominators for this proposed use discussed the use of adding choline to parenteral nutrition.

b. Treatment of Atherosclerosis

No scientific articles evaluating the use of choline chloride for the treatment of atherosclerosis and available in English were cited by the nominator. The nominator included two references for this use that FDA did not review because the articles were in a foreign language[19]: a) 1950 reference by Capretti written entirely in Italian, with the title translated in PubMed as "Lipotrophic Factors and Atherosclerosis; Action of Methionin, Choline and Inositol," and b) 1954 reference by Millot written entirely in French, with the title translated in PubMed as "Action of Lipotropic Factors in Atherosclerosis."[20]

A group of 12 male survivors of acute myocardial infarction were given multiple nutrients (i.e., pyridoxine, folate, cobalamin, choline, riboflavin, and troxerutin) for 21 days. Cholesterol, triglycerides, and LDL apo B declined to 79%, 68% and 63% of pretreatment values respectively (Olszewski et al. 1989).

More recently, one 8-year cohort study failed to show any difference in cardiovascular risk between women in the upper (>329 mg/day) versus lowest (≤ 266 mg/day) quartile of dietary choline intakes (Dalmeijer et al. 2008). The prospective study of the Atherosclerosis Risk in Communities (ARIC) cohort found that the highest versus the lowest quartile of total choline intake from food was not significantly associated with the incidence of coronary artery disease in 14,420 middle-aged participants and that higher choline intake was not protective for coronary heart disease (Bidulescu et al. 2007).

Conclusion: There is insufficient information to support use of choline chloride for the treatment or prevention of atherosclerosis.

c. Treatment of Fetal Alcohol Spectrum Disorder

Optimal maternal nutrition status is required to produce healthy offspring. When maternal nutritional status is compromised with alcohol, essential nutrients are displaced or not obtained. Choline has been classified as an essential nutrient since 1998 (Institute of Medicine 1998; Zeisel 2012).

[19] See also 21 CFR 10.20(c)(2) ("If a part of the material submitted is in a foreign language, it must be accompanied by an English translation verified to be complete and accurate, together with the name, address, and a brief statement of the qualifications of the person making the translation. A translation of literature or other material in a foreign language is to be accompanied by copies of the original publication.").

[20] The 1950 reference by Capretti (written solely in Italian) and the 1954 reference by Millot (written solely in French) were both obtained through the FDA Library; however, no English translations of either publication were located.

In animal models, choline chloride supplementation has reduced some of the detrimental effects of alcohol consumption on fetal animals and the consumption of alcohol is believed to create an extra need for choline by altering one-carbon metabolism, which causes less folate but more choline to be used (Young et al. 2014). However, randomized controlled trials conducted in humans evaluating the use of choline chloride to mitigate adverse effects on infant growth and cognitive function from prenatal alcohol exposure have had mixed results.

We identified two trials evaluating the effect of prenatal choline chloride supplementation to mitigate the adverse effects of prenatal alcohol exposure on the infants:

- A prospective prevention cohort study conducted at two sites in Western Ukraine evaluated the impact of nutritional supplementation during gestation on alcohol exposed infants during their first year (Coles et al. 2015). For that purpose, the study enrolled 301 pregnant women who reported moderate to heavy drinking during their pregnancy, i.e., who reported at least weekly binge drinking (>5 drinks), at least 5 episodes of 3-4 standard drinks or at least 10 episodes of 1-2 standard drinks either in the month around conception or in the most recent month of pregnancy. 313 pregnant women who reported low or no drinking during their pregnancy were enrolled as the control population. The study participants were randomized to one of three treatment groups: (1) no treatment "standard of care", (2) multivitamins and minerals (MVM) supplement group, and (3) MVM plus choline daily treatment containing 750 mg choline or 8 oral gel capsules per day. Because of the significant drop-out rate during the study, the final evaluable sample for infant developmental outcomes included infants of 163 mothers with alcohol use during pregnancy and 204 mothers in the control group.

  The Bayley Scales of Infant Development, 2nd Ed. (BSID-II)[21] to monitor neurodevelopmental outcomes and as an assessment tool for early intervention in young children up to three years of age was used to evaluate effects of the prenatal interventions in alcohol exposed infants compared to infants whose mothers reported low or no drinking during pregnancy. The BSID-II yielded standard scores for Mental Development Index (MDI), Psychomotor Development Index (PDI) and Behavior. The MDI and PDI scores for infants treated with choline and multivitamin/minerals who were not exposed to alcohol during pregnancy were slightly higher compared to the alcohol exposed infants, with almost no difference in scores based on the treatment effect in the group with only MVM supplementation. MVM supplementation was associated with higher scores on cognitive but not psychomotor development. There was no effect of choline on cognitive scores while there was a trend for more negative motor outcome. The trend for behavior scores were similar. The assessments for development delay did not show an improvement in infant outcomes with supplementing choline together with

[21] BSID-II assesses infants between the ages of 1 and 42 months of age using a standardized assessment of children's mental and motor performance and a rating of the child's behavior based on the infant's response to a structured set of stimulus materials. The items are arranged in ordinal sequence of increasing difficulty, representing the maturation of abilities in cognitive and motor development. Raw scores are converted to standardized scores (mean = 100, standard deviation =16) through tables, yielding a Mental Developmental Index (MDI) score from the Mental Scale and a Psychomotor Developmental Index (PDI) score from the Motor Scale. Cut of score of <85 (1.00 SD below mean) represents a clinically meaningful indicator of delayed development on the mental and psychomotor developmental indices.

MVM during pregnancy. Of note, 614 women enrolled in the study and only 136 women reported how frequently they took their assigned treatment. Thus, it is unclear whether the majority of women enrolled in the study took their assigned treatment. The authors' conclusion was that the improved development outcome associated with choline seen in animal models was not observed in the clinical study.

Table 4: Group Means for Infant Developmental Outcomes by Alcohol Use (Etoh) and Supplement Status (MVM)[a] (N = 367): MVM and MVM + C (italicized values)

	Alcohol exposed (n = 163)				Unexposed (n = 204)				Statistic	*p* values
	No supplement (n = 78)	Supplement (n = 85)	*MVM (N = 37)*	*MVM + C (n = 47)*	No supplement (n = 98)	Supplement (n = 106)	*MVM (n = 58)*	*MVM + C (n = 48)*		
Child sex (% male)	42.3 %	48.24 %	*50 %*	*46.8 %*	52.04 %	58.49 %	*58.6 %*	*58.3 %*	EtOH: $\chi^2_{(1)} < 1$	NS
									MVM: $\chi^2_{(1)} < 1$	NS
Birth weight (gms)[b]	3093.27	3180.05	*3218.38*	*3150.43*	3389.94	3403.87	*3470.52*	*3323.33*	EtOH: $F_{(1,361)} = 21.47$	.001
	(547.74)	(616.1)	*(603.64)*	*(630.59)*	(441.84)	(444.72)	*(507.07)*	*(343.37)*	MVM: $F_{(1,361)} < 1$	NS
Birth length (cm)[b]	50.62	51.05	*51.08*	*51.02*	51.97	51.88	*52.03*	*51.69*	EtOH: $F_{(1,361)} = 11.65$	.001
	(3.28)	(3.66)	*(4.02)*	*(3.40)*	(2.27)	(2.25)	*(2.57)*	*(1.81)*	MVM: $F_{(1,361)} < 1$	NS
Birth head circumference (cm)[b]	33.81	33.98	*34.19*	33.81	34.51	34.66	*34.81*	*34.48*	EtOH: $F_{(1,361)} = 13.07$	.001
	(1.95)	(1.94)	*(1.45)*	(2.23)	(1.59)	(1.46)	*(1.59)*	*(1.27)*	MVM: $F_{(1,361)} < 1$	NS
Corrected age at test (weeks)[c]	27.99	28.44	*28.48*	28.17	28.09	28.55	*29.43*	*27.48*	EtOH: $F_{(1,363)} < 1$	NS
	(4.19)	(4.34)	*(5.14)*	(4.52)	(4.35)	(3.97)	*(4.49)*	*(2.97)*	MVM: $F_{(1,363)} < 1$	NS
Bayley Scales-II[d]										
MDI	88.21	89.21	*91.37*	*87.47*	90.65	91.48	*91.05*	*92.00*	EtOH: $F_{(1,362)} = 6.82$	.01
	(9.84)	(10.88)	*(10.16)*	*(11.23)*	(8.39)	(6.37)	*(7.08)*	*(5.46)*	MVM: $F_{(1,362)} < 1$	NS
PDI	88.60	88.00	*90.26*	*86.17*	90.99	89.77	*90.71*	*88.65*	EtOH: $F_{(1,362)} = 2.72$	.10
	(13.42)	(13.96)	*(13.81)*	*(13.96)*	(10.26)	(10.52)	*(10.93)*	*(10.02*	MVM: $F_{(1,362)} < 1$	NS
Orientation/engagement (n = 349)	20.93	24.54	*24.68*	*24.43*	26.48	25.79	*24.69*	*27.15*	EtOH: $F_{(1,347)} = 3.47$	.06
	(14.25)	(18.43)	*(15.51)*	*(20.49)*	(17.24)	(17.22)	*(17.12)*	*(17.44)*	MVM: $F_{(1,347)} = 1.09$	NS
Emotional reactivity (n = 349)	43.65	46.20	*45.97*	*46.37*	48.13	45.42	*47.12*	*43.32*	EtOH: $F_{(1,347)} < 1$	NS
	(26.39)	(25.68)	*(25.11)*	*(26.37)*	(25.49)	(24.82)	*(25.81)*	*(23.65)*	MVM: $F_{(1,347)} < 1$	NS
Motor quality	16.36	17.53	*18.94*	*15.20*	20.18	20.91	*20.24*	*21.96*	EtOH: $F_{(1,363)} = 4.99$	.03
	(13.54)	(15.76)	*(16.82)*	*(14.62)*	(15.49)	(16.61)	*(15.82)*	*(17.83)*	MVM: $F_{(1,363)} < 1$	NS
Total behavior quality	20.58	24.34	*24.74*	*22.67*	25.16	24.68	*24.43*	*25.06*	EtOH: $F_{(1,363)} = 1.75$	NS
	(16.42)	(19.32)	*(18.17)*	*(19.84)*	(17.18)	(18.16)	*(18.26)*	*(18.3)*	MVM: $F_{(1,363)} < 1$	NS

[a] Collapsing across choline; italicized values: without collapsing across choline

[b] Multivariate analysis controlling for child sex [birthweight: $F_{(1,361)} = 4.55$, $p < .03$; birth length: $F_{(1,361)} = 4.41$, $p < .04$; birth head circumference: $F_{(1,361)} = 4.44$, $p < .05$]

[c] Corrected for gestational age at birth

[d] Multivariate analysis of variance

Source: Table 2; Coles et al. 2015.

Maternal choline blood levels were measured at recruitment and in the third trimester. A separate multivariate analysis using alcohol group and supplement status (None, MVM and MVM + choline) found no differences among maternal choline blood levels pre and post supplementation or on the standardized difference score.

A weakness of this study is that it does not clarify whether choline supplementation alone would have resulted in similar changes since the treatment group receiving choline also received a multivitamin/mineral supplement. Because the Ukraine does not engage in folic acid enrichments of their food products, as do many other countries, the changes seen in the infants in the choline/MVM group might have been solely due to the MVM.

- In an exploratory, randomized, double-blind, placebo-controlled clinical trial, 69 heavy drinkers (at least >2 drinks/day) in Cape Town, South Africa, recruited in mid-pregnancy, were randomly assigned to receive a daily oral dose of either 2 g of choline or placebo

from time of enrollment until delivery (Jacobson et al. 2018). The primary outcome was eyeblink conditioning (EBC)[22] assessed when the infants were 6.5 months. Somatic growth was also measured at birth, 6.5 months and 12 months and recognition memory and processing speed on the Fagan Test of Infant Intelligence was assessed at 6.5 months and 12 months.

For the purposes of analysis, there were 48 infants with usable EBC data. The author acknowledges that a larger proportion of the choline group met criterion for conditioning compared with the placebo group, although the effect fell short of conventional levels of statistical significance as shown in Table 5.

Table 5: Effects of Choline Supplementation on Eyeblink Conditioning

	Whole sample			Adherence[a] >20%		
	Choline	Placebo	Total	Choline	Placebo	Total
Fail	9	17	26	6	17	23
	40.9%	65.4%	54.2%	33.3%	65.4%	52.3%
Pass	13	9	22	12	9	21
	59.1%	34.6%	45.8%	66.7%	34.6%	47.7%
Total	22	26	48	18	26	44
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	$\chi^2 = 2.88$, $p = 0.090$			$\chi^2 = 4.38$, $p = 0.036$		

[a]Adherence to supplementation protocol.

Source: Table 2; Jacobson et al. 2018.

Although the authors concluded that infants born to choline-treated mothers "were more likely to meet criterion for conditioning on EBC than the placebo group" it is not clear what the changes in EBC mean when interpreting neurodevelopmental outcomes in these infants. Infants born to mothers who were supplemented with choline during pregnancy showed catch-up growth in weight and head circumference at 6.5 and 12 months compared to the placebo treated infants in whom the percentiles for weight, length, and head circumference decreased from birth to 6.5 months. At 12 months, the infants in the choline treatment arm had higher preferential looking at the novel stimulus (novelty preference scores) on Fagan Test of Infant Intelligence, indicating better visual recognition memory.

We also identified two trials in which choline was evaluated in children for the treatment of fetal alcohol syndrome:

- In a 6-week multisite, randomized, double-blinded, placebo-controlled, parallel-group clinical trial in children with fetal alcohol spectrum disorders, Glycerophosphocholine liquid (Nutrasal dietary supplement) containing 625 mg choline (N = 29) or placebo (N = 26) was administered daily to children aged 5-10 years of age. Participants in the

[22] Eyeblink conditioning (EBC) is a classical conditioning paradigm typically used to study the underlying neural processes of learning and memory that involves contingent temporal pairing of a conditioned stimulus (e.g., auditory tone) with an unconditioned stimulus (e.g., air puff). EBC is used a research tool and in infants shortly after birth.

choline group did not improve in cognitive performance in any domain compared with placebo (Nguyen et al. 2016).

No serious adverse events (SAEs) were reported; however, the number of children who reported at least 1 AE was significantly higher in the choline group (23/29) than in the placebo group (13/26). Minimal AEs information was provided. The one AEs table in the publication reported the total number of participants who reported any of eight high-level categories of AEs, e.g., "general health," "skin," "allergy." For example, from this table it could be noted that 12 children on choline versus 7 children on placebo reported at least one gastrointestinal adverse event; however, this type of high-level information is not particularly helpful in assessing the safety of choline.

- A double-blind, randomized, placebo-controlled pilot study by Wozniak et al. (2015) was conducted in 60 children aged 2.5-5 years at enrollment with fetal alcohol spectrum disorders (FASD). They received either a liquid choline supplement (choline bitartrate 1.25 grams containing 500 mg choline; n=31) or placebo (n=29) once daily for 9 months. Outcome measures were Mullen Scales of Early Learning (primary) and elicited imitation (EI) memory paradigm (secondary).

  The study failed on the primary endpoint of global cognitive ability. Choline supplementation improved the secondary outcome EI only after immediate recall performance was controlled for and the outcome was moderated by age. The largest improvement in delayed EI performance was in the young choline group (aged 2.5 to ≤ 4.0-year-olds at enrollment; n=16). No SAEs were reported. The only AE linked to choline was fishy body odor (reported by 15 of the 31 subjects treated with choline versus no subjects on placebo).

Conclusion: There is insufficient information to support use of choline chloride for the treatment of fetal alcohol syndrome.

d. Supplementation in long term total parenteral nutrition

Choline deficiency frequently occurs in long-term total parenteral nutrition patients, i.e., 52% were markedly low, 33% low, and 14% normal in one study (Compher et al. 2002). Lipid emulsions administered to patients on total parenteral nutrition increase their plasma-free choline concentrations; however, they do not increase the choline concentrations to normal (Sheard et al. 1986; Buchman 2006).

In 2012, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) published a position paper recommending that choline be routinely added to adult and pediatric parenteral nutrition (PN) formulations and stating that a commercially available parenteral product needed to be developed (Vanek et al. 2012). This same publication contains the following recommendations regarding parenteral choline:

- Provide 550 mg/day of choline routinely to adult PN formulations (requires development of either an individual choline product or addition of choline into either a multiple vitamin or trace element product)
- Recommend routine parenteral administration in newborns and pediatric patients with the following dosing:
  - 0–6 months: 125 mg/day
  - 7–12 months: 150 mg/day
  - 1–3 years: 200 mg/day
  - 4–8 years: 250 mg/day
  - 9–13 years: 375 mg/day
  - >13 years: adult amounts

Conclusion: We were not able to find data regarding the extent of use of choline chloride in parenteral nutrition, if it is in fact added to parenteral nutrition. Although the A.S.P.E.N has made this recommendation, it is not clear that it has been implemented in the treatment of patients on total parenteral nutrition. Accordingly, there is insufficient information on the effectiveness of choline chloride for supplementation in long term parenteral nutrition.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Choline chloride is being evaluated for the treatment of hepatic steatosis/NAFLD, fetal alcohol spectrum disorder, atherosclerosis, and for supplementation in total parenteral nutrition.

- In some cases of NASH, patients can progress to cirrhosis and develop liver cancer.
- Fetal alcohol syndrome can result in serious cognitive, physical, and behavioral impairments.
- Atherosclerosis can be serious and life threatening.
- Parenteral nutrition is necessary in different clinical situations in which the patient needs supplemental calories and nutrients in addition to their enteral calorie intake or may be completely dependent on parenteral nutrition. Many patients requiring parenteral nutrition are suffering from serious conditions.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

If the patient can digest and absorb oral foods, it is anticipated that dietary intake of choline would be as effective as the use of oral choline chloride preparations.

No FDA-approved drug treatments currently exist for NAFLD. Lifestyle changes (e.g., weight loss, exercise, and avoidance of alcoholic beverages) are often recommended by healthcare providers for patients with liver disease. For patients with cirrhosis due to nonalcoholic steatohepatitis, liver transplantation may be an option.

Multiple therapies have been approved for the treatment of atherosclerosis including antiplatelet medications (to prevent the build-up of plaque, help prevent blood clots), angiotensin-converting

enzyme inhibitors (to lower blood pressure), and medications to lower cholesterol including statins (e.g., atorvastatin[23], lovastatin[24], pravastatin[25], simvastatin[26]), fibrates (e.g., gemfibrozil[27], fenofibrate[28]), niacin[29], ezetimibe[30], bile acid sequestrants (e.g., cholestyramine[31]) and PCSK9 inhibitors (evolocumab[32], alirocumab[33]). Angioplasty and coronary artery bypass grafting are surgeries that can improve blood flow to the heart.

While no therapies have been approved to treat fetal alcohol syndrome, medications for specific symptoms associated with fetal alcohol syndrome, e.g., hyperactivity, inability to focus or anxiety, can assist in managing these symptoms.

Sources of choline for parenteral nutrition are available as egg phospholipid in approved lipid products which is primarily phosphatidylcholine or phosphatidylethanolamine (e.g. Intralipid 20%[34]). The body can convert each to choline through metabolic pathways.

Conclusions: We did not find clinical information that supported the effectiveness of choline chloride, including the nominator's proposed dosage form with route of administration using parenteral injection, for the proposed uses with respect to: liver diseases (including NAFLD), hepatic steatosis, atherosclerosis, and fetal alcohol syndrome. There is insufficient information on the effectiveness of choline chloride for supplementation in long term parenteral nutrition. Currently approved lipid emulsions are a source of calories and essential fatty acids for parenteral nutrition and contain a source of choline in the form of phosphatidylcholine and phosphatidylethanolamine.

D. Has the substance been used historically in compounding?

Databases searched for information on choline chloride in regard to Section II.D. of this consultation included PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

FDA also considered the report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) (M-CERSI 2019, Appendix 2).

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[23] See Atorvastatin at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 020702).
[24] See Lovastatin at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 021316).
[25] See Pravastatin at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 019898).
[26] See Simvastatin at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 019766).
[27] See Gemfibrozil at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 018422).
[28] See Fenofibrate at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 021695).
[29] See Niacin at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 020381).
[30] See Ezetimibe at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., NDA 021445).
[31] See Cholestyramine at https://www.accessdata.fda.gov/scripts/cder/daf/. (e.g., ANDA 073263).
[32] See Evolocumab at https://www.accessdata.fda.gov/scripts/cder/daf/. (BLA 125522).
[33] See Alirocumab at https://www.accessdata.fda.gov/scripts/cder/daf/ (BLA 125559).
[34] Intralipid (soybean oil) is an FDA approved drug product, available in 10%, 20%, and 30% strengths. See Intralipid at https://www.accessdata.fda.gov/scripts/cder/daf/ (e.g., NDA 017643).

1. *Length of time the substance has been used in pharmacy compounding*

Choline was discovered in the late 1800's and was officially recognized as an essential nutrient by the Institute of Medicine in 1998 (Institute of Medicine 1998; Zeisel 2012). Based on published literature, choline chloride has been used in pharmacy compounding since at least 1954 (Coxon and Kolb 1954).

2. *The medical condition(s) it has been used to treat*

According to the Natural Medicines Database, choline (not choline chloride) is used orally for hepatitis, NAFLD, and cirrhosis, among multiple other conditions (Natural Medicines Comprehensive Database 2021). It is unknown whether choline chloride is typically compounded into a drug product when used for the conditions above or whether, for example, a dietary supplement of choline chloride is typically used.

Through a literature search, M-CERSI identified seven articles that utilized a compounded choline chloride product for various conditions including the following: hepatic steatosis, verbal and visual memory improvement, cystinuria, Huntington's disease, tardive dyskinesia, manic-depressive illness, schizophrenia, and lipotrophic states in cardiovascular disease. Four of the studies utilized choline chloride as an intravenous or intramuscular injection and three studies used an oral solution (M-CERSI 2019, Appendix 2).

In a survey conducted by M-CERSI regarding choline chloride utilization among various healthcare practitioners (Doctor of Medicine, Naturopathic Doctor, Doctor of Pharmacy), two of 29 responders reported using, prescribing, or recommending choline chloride products. One respondent used choline chloride 50 mg in combination with inositol 50 mg and L-methionine 25 mg for "fat metab."

Results from a Google search using the terms *choline chloride compounding pharmacy* indicate that choline chloride is/has been included in combination with other ingredients in compounded injectable products for weight loss in the United States (US). It appears that choline chloride is often combined with methionine and inositol, two other amino acids, and the combination is known as "MIC."

The International Journal of Pharmaceutical Compounding (IJPC) published a formulation for an injection consisting of methionine, inositol, choline chloride, methylcobalamin, chromium chloride hexahydrate, benzyl alcohol, and sterile water for injection for weight loss (Williams 2010). In addition, IJPC published a formulation for an injection consisting of cyanocobalamin, choline chloride, niacinamide, benzyl alcohol, glacial acetic acid, and sterile water for injection for use "as a vitamin/nutritional supplement" (Loyd 2010).

3. *How widespread its use has been*

Insufficient data are available from which it is possible to draw conclusions about the extent of use of choline chloride in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

A search of the British Pharmacopoeia (BP 2020), the European Pharmacopoeia (10th Edition 10.0), and the Japanese Pharmacopoeia (17th Edition) did not show any monograph listings for choline chloride.

Ketovite Liquid, containing 2,500 IU vitamin A palmitate, 400 IU ergocalciferol, 12.5 µg cyanocobalamin, and 150 mg choline chloride in each 5 mL, has market authorization in the U.K. from the Medicines and Healthcare products Regulatory Agency (MHRA).[35] In the U.K., Ketovite Liquid is indicated for the prevention of vitamin deficiency in conditions such as galactosaemia, disaccharide intolerance, phenylketonuria, in other disorders of starch, sugar or amino acid metabolism, and in patients who are on restricted, specialized or synthetic diets (Medicines and Healthcare Products Regulatory Agency 2021).

Conclusions: The available evidence indicates that choline chloride has been used in pharmacy compounding since at least 1954. Based on advertising information, choline chloride is most often used in compounded injectable products for weight loss in the US. Choline chloride is available in the United Kingdom as part of a multiple ingredient product, Ketovite Liquid, indicated for the prevention of vitamin deficiency in certain conditions.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate choline chloride for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** choline chloride being placed on that list based on the following:

1. Choline chloride is a small molecule. The nominated compound is easily characterized with various analytical techniques and the preparation of this compound has been well developed. It is likely to be stable under ordinary storage conditions in solid and liquid formulations.

2. Choline is a constituent in food and is made endogenously in the body. When administered in amounts much greater than typically ingested in the diet, it can lead to adverse effects, e.g., nausea, vomiting, diarrhea, headache, anxiety, restlessness, and hypotension.

3. Although there are many mechanistic articles in the literature purporting a benefit in a variety of diseases, we were not able to find clinical effectiveness data to support the proposed use of choline chloride with respect to: liver diseases (including NAFLD), hepatic steatosis, atherosclerosis, and fetal alcohol syndrome. Theoretically, patients who were to consume a diet deficient in choline could develop NAFLD; however, since the US diet is rich in choline-containing foods, patients are unlikely to need a

[35] MHRA regulates medical products in the United Kingdom.

change in their diet in order to include choline-rich foods. We could not find clinical evidence that choline chloride administration will be effective in the treatment of NAFLD that is not related to a deficiency of choline. There is insufficient information on the effectiveness of choline chloride for supplementation in long term parenteral nutrition. Current parenteral nutrition sources of choline are available as egg phospholipid in approved lipid products.

4. Choline chloride has been used in pharmacy compounding since at least 1954. Based on advertising information, choline chloride is most often used in compounded injectable products for weight loss in the US. Choline chloride is available in the United Kingdom as part of a multiple ingredient product, Ketovite Liquid, indicated for the prevention of vitamin deficiency in certain conditions.

Based on this information the Agency has considered, a balancing of the four evaluation criteria weighs against choline chloride being added to the 503A Bulks List.

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APPENDIX 1: NIH Office of Dietary Supplements, Choline Fact Sheet for Health Professionals[36]

[36] Accessed on 3/16/2021 at https://ods.od.nih.gov/factsheets/Choline-HealthProfessional/#en11

Table: Selected Food Sources of Choline[37]

Food	Milligrams (mg) per serving	Percent DV*
Beef liver, pan fried, 3 ounces	356	65
Egg, hard boiled, 1 large egg	147	27
Beef top round, separable lean only, braised, 3 ounces	117	21
Soybeans, roasted, ½ cup	107	19
Chicken breast, roasted, 3 ounces	72	13
Beef, ground, 93% lean meat, broiled, 3 ounces	72	13
Fish, cod, Atlantic, cooked, dry heat, 3 ounces	71	13
Potatoes, red, baked, flesh and skin, 1 large potato	57	10
Wheat germ, toasted, 1 ounce	51	9
Beans, kidney, canned, ½ cup	45	8
Quinoa, cooked, 1 cup	43	8
Milk, 1% fat, 1 cup	43	8
Yogurt, vanilla, nonfat, 1 cup	38	7
Brussels sprouts, boiled, ½ cup	32	6
Broccoli, chopped, boiled, drained, ½ cup	31	6
Mushrooms, shiitake, cooked, ½ cup pieces	27	5
Cottage cheese, nonfat, 1 cup	26	5
Fish, tuna, white, canned in water, drained in solids, 3 ounces	25	5
Peanuts, dry roasted, ¼ cup	24	4
Cauliflower, 1" pieces, boiled, drained, ½ cup	24	4
Peas, green, boiled, ½ cup	24	4
Sunflower seeds, oil roasted, ¼ cup	19	3
Rice, brown, long-grain, cooked, 1 cup	19	3
Bread, pita, whole wheat, 1 large (6½ inch diameter)	17	3
Cabbage, boiled, ½ cup	15	3
Tangerine (mandarin orange), sections, ½ cup	10	2
Beans, snap, raw, ½ cup	8	1
Kiwifruit, raw, ½ cup sliced	7	1
Carrots, raw, chopped, ½ cup	6	1
Apples, raw, with skin, quartered or chopped, ½ cup	2	0

*DV = Daily Value. The U.S. Food and Drug Administration (FDA) developed DVs to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for choline is 550 mg for adults and children age 4 years and older [12]. FDA does not require food labels to list choline content unless choline has been added to the food. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.

[37] U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019.

APPENDIX 2: University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI) report on choline chloride

Summary Report

Choline Chloride

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

December 2019

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REVIEW OF NOMINATIONS

Choline chloride (UNII code: 45I14D8O27) was nominated for inclusion on the 503B Bulks List by Fagron, American College for Advancement in Medicine (ACAM), McGuff Compounding Pharmacy Services, Inc, American Association of Naturopathic Physicians (AANP), Alliance for Natural Health USA (ANH-USA), and Integrative Medicine Consortium (IMC).

Choline chloride was nominated for oral and intravenous use. Orally choline chloride is used in liver disease including chronic hepatitis and cirrhosis; hypercholesterolemia; depression; memory loss; Alzheimer's disease and dementia; schizophrenia; body building; delaying fatigue in endurance sports; preventing neural tube defects; preventing cancer; Huntington's chorea; Tourette's disease; cerebellar ataxia; complex partial seizures; asthma; and as a supplement in infant formulas. Intravenously choline chloride is used for TPN-associated hepatic steatosis, choline deficiency, and fetal alcohol syndrome.

The nominated formulations include a 0.1 mg/mL injection, a 25-100mg/mL injection, and an injection in various concentrations and formulations in combination with other vitamins, supplements, and/or minerals, refer to Table 7 for the nominated combination formulas. Choline chloride will be administered via intravenous or intramuscular injection.

Reasons provided for nomination to the 503B Bulks List include:

- There are no FDA-approved injectable products containing choline chloride as a single active pharmaceutical ingredient (API) or in combination with other APIs.
- There are no FDA-approved medications to treat choline deficiency.
- Thousands of patients with metabolic disorders are prescribed and use choline chloride as a single preparation or a combination preparation by alternative and naturopathic physicians.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of choline chloride products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA) and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for choline chloride; name variations of choline chloride were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing choline chloride. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through September 7, 2018. The search included a combination of (choline[TIAB] OR "choline chloride"[TIAB] OR "choline hydrochloride"[TIAB] OR "cholinium chloride"[TIAB]) AND (therapy[TIAB] OR therapeutic[TIAB] OR treatment[TIAB] OR hepat*[tiab] OR "non-alcoholic fatty liver disease"[TIAB] OR atherosclerosis[TIAB] OR "fetal alcohol spectrum disorder"[TIAB] OR ped*[TIAB] AND (humans[MeSH Terms] AND English[lang]) NOT autism). Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of choline chloride or the implementation of choline chloride in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

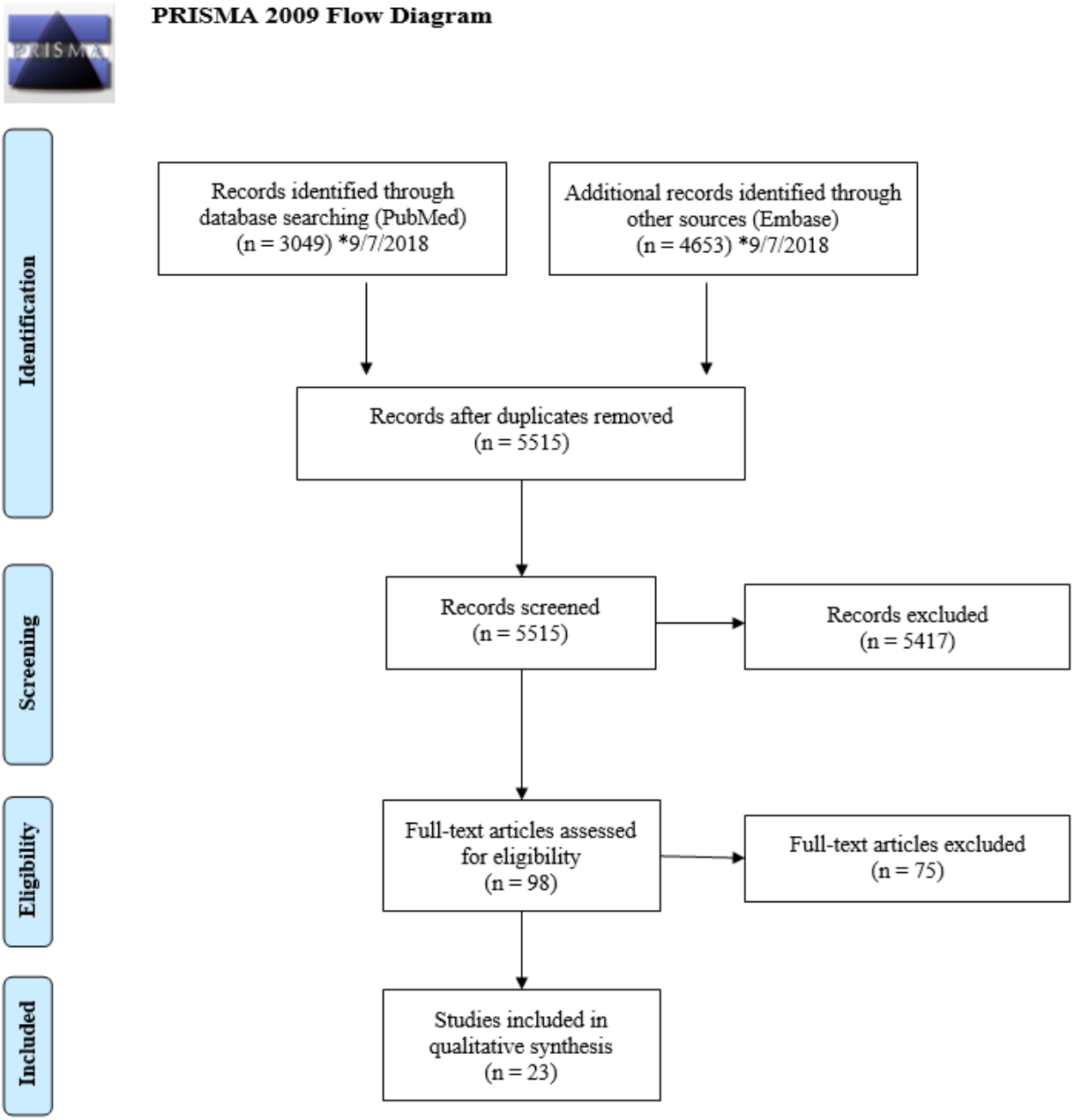
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for choline chloride use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of choline chloride compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, nine (9) medical specialties that would potentially use choline chloride were identified: cardiology, hematology, hepatology, naturopathy, neurology, pediatrics, psychiatry, primary care, and pulmonology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. To determine if a formal interview was warranted, medical experts in hepatology, neurology, and psychiatry were provided the list of substances pertinent to their specialty via email. The hepatogolist and the psychiatrist replied that they do not utilize any of the substances listed. The neurologist failed to respond to the interview request. One (1) expert was contacted for an interview, of which one (1) accepted and zero (0) declined interviews. The interview was recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for cardiology, hematology, hepatology, naturopathy, neurology, pediatrics, psychiatry, primary care, and pulmonology, identified from the nominations, literature review, and interviews, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to twelve (12) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Naturopathy	American Association of Naturopathic Physicians (AANP)
Pediatrics	American Academy of Pediatrics (AAP)
Primary Care	American Association of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Hematology	American Society of Hematology (ASM)	Failed to respond
Hepatology	American Association for the Study of Liver Diseases (AASLD)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Primary Care	American College of Physicians (ACP)	Failed to respond
	American Academy of Family Physicians (AAFP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, "we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products"
Pulmonology	American Thoracic Society (ATS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Choline chloride is not available as an FDA-approved product.
- Choline chloride is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) dietary monograph for choline chloride.
- Choline chloride is not available in any of the foreign regulatory databases searched.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and region

Summary of literature review

- Total number of studies included: 23 studies (6 descriptive, 14 experimental, and 3 observational).
- Most of the studies were from the US (14 studies).
- The most common indication in the US was for tardive dyskinesia followed by memory impairment in the elderly and then hepatic steatosis and Huntington's disease. From the non-US studies, the most common indication was cerebellar and spinocerebellar ataxia.
- There were no combination products found identical to the nominator's example combination. One (1) non-nominated combination was found consisting of choline chloride 100mg / folic acid 2mg / heparin sodium 25mg / niacinamide 50mg / vitamin B_{12} 15 mcg.
- There were six (6) US studies with compounded products identified for hepatic steatosis, verbal and visual memory improvement, cystinuria, Huntington's disease, tardive dyskinesia, manic-depressive illness, schizophrenia, and lipotrophic states in cardiovascular disease. Four (4) of the studies utilized choline chloride as an intravenous or intramuscular injection and two (2) studies used and oral solution. One (1) non-US study used a 0.1% oral solution as a compounded product for Huntington's disease.

Table 5. Types of studies

Types of Studies	**Number of Studies**
Descriptive[1-6]	6
Experimental[7-20]	14
Observational[21-23]	3

Table 6. Number of studies by country

Country	Number of Studies
Chile[16]	1
Germany[8]	1
India[15]	1
Japan[6]	1
Sweden[7]	1
The Netherlands[2]	1
UK[3,13,14]	3
US[1,4,5,9-12,17-23]	14
Total US: 14 Total non-US Countries: 9	

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Choline chloride 50mg / Inositol 50mg / L-methionine 25mg	0
Others found in literature	Choline chloride 100mg / Folic acid 2mg / Heparin sodium 25mg / Niacinamide 50mg / Vitamin B_{12} 15 mcg[19]	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Tardive dyskinesia[1,12,22,23]	150-200mg/kg/day	–	–	Oral	6-8 weeks
	4-20g/day	0.5g/mL	–		29-56 days
Memory impairment in elderly[5,17,20]	9-20g/day	–	–	Oral	7-28 days
Hepatic steatosis[9,10]	1-4g/day	50%	Solution	Intravenous	6-24 weeks
Huntington's disease[22,23]	4-20g/day	0.5g/mL	Solution	Oral	29-40 days
Cystinuria[21]	3-8g/day	25%	Elixir	Oral	–
Hepatic cirrhosis[4]	1.5-6g/day	–	–	–	–
Infectious hepatitis[4]	20g/day	–	–	–	2-3 weeks
Korsakoff's syndrome[18]	10.4-18.2g/day	–	–	Oral	3 weeks
Lipotrophic states in cardiovascular disease[19]	2mL	0.1g/mL	Injection	Intramuscular	As needed
Manic-Depressive Illness[22]	4-20g/day	0.5g/mL	–	–	29-40 days
Pernicious anemia[4]	1g/day	5%	Solution	Intravenous	–
Schizophrenia[22]	4-20g/day	0.5g/mL	–	–	29-40 days
Verbal and visual memory improvement[11]	2g/day	–	Solution	Intravenous	24 weeks

Abbreviations: "–", not mentioned; ROA, route of administration

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cerebellar[6,13] and spinocerebellar ataxia[14]	4-12g/day	–	–	Oral	6-12 weeks
	150mg/kg/day			–	–
Asthma (immune inflammation and bronchial hyperreactivity)[15]	3g/day	–	–	Oral	6 months
Edema[2]	3g/day	–	–	Oral	14 days
Hepatic steatosis[8]	3g/day	1g	–	Oral	90 days
Huntington's disease[7]	3-15g/day	–	Solution	Oral	–
Megalobastic anemias[3]	3-10g/day	–	Solution	Oral	–
	1-10g/day	–		Intravenous	16 days
Nutritional dystrophy[16]	0.32g/day	–	–	Oral	1-53 days

Abbreviations: "–", not mentioned; ROA, route of administration

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Hepatic steatosis[9,10]	2005, 1995	• Choline chloride 1-4g added to total parenteral nutrition (TPN)	Solution	–
Verbal and visual memory improvement[11]	2000	• Choline chloride 2g added to TPN	Solution	–
Cystinuria[21]	1954	• Choline chloride 250g • Distilled water 150mL • Raspberry syrup 1000mL	Solution	25%
Huntington's disease, tardive dyskinesia, manic-depressive illness, schizophrenia[22]	1978	• Dissolved in distilled water and flavored with strawberry syrup	Solution	0.5g/mL
Lipotrophic states in cardiovascular disease[19]	1955	• "Hep-Nine B prepared by The Columbus Pharmacal Company, Columbus, Ohio" • Each cc contains: o Heparin Sodium (2500 units) 25mg o Choline Chloride 100mg o Vitamin B_{12} 15mcg o Folic Acid 2mg o Niacinamide 50mg	Solution	100mg/mL

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Huntington's disease[7]	• Choline chloride: 100 mg • Liquor pectoralis: 60 mL • Distilled water: to 1000 mL	Solution	0.1%

Summary of focus groups/interviews of medical experts and specialty organizations

Two (2) interviews were conducted with the same person. A Medical Doctor (MD) specializing in hepatology, an MD specializing in psychiatry, and an MD specializing in psychiatry were provided the list of substances pertinent to their specialty via email, which included choline chloride. Per the hepatologist, choline chloride has no indication in liver disease. The psychiatrist does not use choline chloride. The neurologist failed to respond to the interview request.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Choline Chloride	Interview Summary Response
NAT_01B, NAT_02	ND	None	Private practice	Yes	• Sometimes uses supplements like lecithin or phosphatidylcholine that contains choline chloride; more experience with choline only.

Abbreviation: ND, Naturopathic Doctor

- Use of choline chloride
    - Interviewee stated "we use that [choline chloride] in our brain IVs, so IV form, and then we would use it for neurodegenerative illnesses, and then as a repletion if we do a vitamin/mineral analysis."
    - Uses in an IV formulation for antiaging
    - Uses supplements, like lecithin or phosphatidylcholine, that contain choline chloride
- Administration of choline chloride
    - Intravenous administration
    - Weight-based dosing
- Need for office-stock
    - Interviewee stated stocks in office however did not supply any additional details regarding the need

Summary of survey results

Table 13. Characteristics of survey respondents [29 people responded to the survey[a]]

Board Certification	MD	ND	PharmD	No Response
Anesthesiology	7	0	0	0
Critical Care Medicine	3	0	0	0
Clinical Pharmacology	1	0	0	0
Gastroenterology	1	0	0	0
Fellow of the American Board of Naturopathic Oncology	0	1	0	0
Hospice & Palliative Medicine	1	0	0	0
Naturopathic Doctor	0	6	0	0
Naturopathic Physician	0	5	0	0
Pediatrics	4	0	0	0
Pediatric Anesthesiology	3	0	0	0
No Board Certification	1	2	1	0
No Response	0	0	0	7

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy

[a]Some respondents reported more than one terminal clinical degree or board certification.

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=2[a])
Compounded	1[b]
FDA-approved	0
Over-the-counter	0
Dietary	1
Unsure	0
No response	0

[a]Out of 29 respondents, two (2) reported using, prescribing, or recommending choline chloride products.
[b]One (1) respondent used in combination: "Choline chloride 50mg / Inositol 50mg / L-methionine 25mg".

Table 15. Compounded use of choline chloride in practice

No survey respondents provided this information

Table 16. Indications for which choline chloride is considered a standard therapy

Indication	Standard Therapy	
	Compounded, n (N=1)	Non-Compounded, n (N=1)
Prenatal support	0	1
No response	1	0

Table 17. Reasons for using a compounded product instead of any FDA-approved products

Reasons
"fat metab"

Table 18. Change in frequency of compounded choline chloride usage over the past 5 years

	Respondents, n (N=1)
No - use has remained consistent	0
Yes - I use it LESS often now	0
Yes - I use it MORE often now	1

Table 19. Do you stock non-patient specific compounded choline chloride in your practice?

	Respondents, n (N=1)
No	1
Yes	0

Table 20. Questions related to stocking non-patient specific compounded choline chloride

No survey respondents provided information for this section

CONCLUSION

Choline chloride (UNII code: 45I14D8O27) was nominated for inclusion on the 503B Bulks List for oral and intravenous use. Orally choline chloride is used in liver disease including chronic hepatitis and cirrhosis; hypercholesterolemia; depression; memory loss; Alzheimer's disease and dementia; schizophrenia; body building; delaying fatigue in endurance sports; preventing neural tube defects; preventing cancer; Huntington's chorea; Tourette's disease; cerebellar ataxia; complex partial seizures; asthma; and as a supplement in infant formulas. Intravenously choline chloride is used for TPN-associated hepatic steatosis, choline deficiency, and fetal alcohol syndrome.

The nominated formulations include a 0.1 mg/mL injection, a 25-100mg/mL injection, and an injection in various concentrations and formulations in combination with other vitamins, supplements, and/or minerals, refer to Table 7 for the nominated combination formulas. Choline chloride will be administered via intravenous or intramuscular injection. Choline chloride was not available in any of the foreign regulatory databases searched.

From the literature review conducted, the most common indications in the US were for tardive dyskinesia followed by memory impairment in the elderly, hepatic steatosis, and Huntington's disease. From the non-US studies, the most common indications were cerebellar and spinocerebellar ataxia. There were no combination products found identical to the nominator's example combination. There were six (6) US studies with compounded products identified for hepatic steatosis, verbal and visual memory improvement, cystinuria, Huntington's disease, tardive dyskinesia, manic-depressive illness, schizophrenia, and lipotrophic states in cardiovascular disease. Four (4) of the studies utilized choline chloride as an intravenous or intramuscular injection and two (2) studies used and oral solution. One (1) non-US study used a 0.1% oral solution as a compounded product for Huntington's disease.

From the interviews, the interviewee sometimes used supplements like lecithin or phosphatidylcholine that contain choline chloride. The hepatologist and psychiatrist contacted both stated that they do not use choline chloride.

From the survey responses, two (2) out of 29 respondents used choline chloride. One (1) respondent reported using compounded choline chloride in combination with inositol 50mg and L-methionine 25mg.

APPENDICES

Appendix 1. References

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Appendix 2. Transcripts from focus groups/interviews

INTERVIEW 1 NAT 01B

Interviewer 1: Okay. I forgot. I lost my train of thought. What about choline chloride? How do you use that particular substance?

NAT_01B: Choline chloride?

Interviewer 1: Yes.

NAT_01B: We use that in our brain IVs, so IV form, and then we would use it for neurodegenerative illnesses, and then as a repletion if we do a vitamin/mineral analysis. Are you saying choline?

Interviewer 1: Choline, yes, yes, yeah.

NAT_01B: Choline. Okay. Yeah, yeah, yeah. Okay. I wanted to say it right.

Interviewer 1: Okay.

NAT_01B: I was just making sure.

Interviewer 1: Yeah.

NAT_01B: Then antiaging. Yeah.

Interviewer 1: So, IV for antiaging. Do you use IV as well, or is there a different dosage form?

NAT_01B: Yes.

Interviewer 1: Mostly IV for that medication?

NAT_01B: Yes. Mm-hmm (affirmative).

Interviewer 1: So, would that be something that you would stock in your office as well?

INTERVIEW 1 NAT 02

Interviewer 1: Okay. So, like I had mentioned the last time that we talked, we have done kind of a literature review to see what's out there about these different substances, and so now we just kind of want to see where it fits into clinical practice. In terms of Choline chloride, what would you consider to be the major indications or conditions that you use Choline chloride for?

NAT_02: Choline chloride... That's the one I don't use often.

Interviewer 1: Oh Okay.

NAT_02: Yeah I don't. Let's see. I need my lab notes. I don't ... I use choline. I don't use choline chloride.

Interviewer 1: Okay.

NAT_02: But I mean, lecithin?

Interviewer 1: Okay.

NAT_02: You know the supplement lecithin?

Interviewer 1: Yeah.

NAT_02: Choline chloride's in that.

Interviewer 1: Yes yes.

NAT_02: So, I would just ... I mean, it would be kind of a side. I don't use that one specifically. I use lecithin.

Interviewer 1: Okay. So then, and then, this just happens to be in the product that you prescribe or recommend?

NAT_02: Right, like phosphatidylcholine. I would recommend that.

Appendix 3. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **choline chloride**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Choline chloride

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q14 If What type(s) of product(s) do you use, prescribe, or recommend for choline chloride? Please check all th... != Compounded drug product

Skip To: Q3 If What type(s) of product(s) do you use, prescribe, or recommend for choline chloride? Please check all th... = Compounded drug product

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for choline chloride? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q6 If Do you use compounded choline chloride as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded choline chloride as a single agent active ingredient, or as one active ingredient... = Combination

Q4. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

- ☐ Choline chloride 50mg / Inositol 50mg / L-methionine 25mg
- ☐ Other (please describe)_____

Q5. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?_____

Q6. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why)_____
- ○ Yes - I use it **LESS** often now (briefly describe why)_____
- ○ No - use has remained consistent

Q8. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

- o Yes
- o No

Skip To: End of Block If Do you stock non-patient-specific compounded choline chloride in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded choline chloride in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded choline chloride? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded choline chloride? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded choline chloride? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

_____

Q14. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources? _____

End of Block: Choline chloride

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information

Appendix 4. Raw survey data

See attached PDF for raw survey data.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [ ] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [ ] Reduced l-glutathione
- [ ] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

neuropathy, diabetes

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

hypertension, general antioxidant, diabetes, heart disease

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

PCOS, NAFLD, DIABETES

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

YES

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ]

- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [ ] Reduced l-glutathione
- [ ] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

neurological, diabetes

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

to replenish what's lost for statin therapies, heart disease, kidney disease, fatigue, diabetes

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

insomnia, infertility and obsessive compulsive disorder, other mental health conditions

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

joint pain and skin integrity

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

yes

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ]

- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [x] Choline chloride
- [ ] Citrulline
- [ ] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age,

gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

cancer

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why)
- ◉ Yes - I use it **LESS** often now (briefly describe why)
- ○ No - use has remained consistent

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

quality

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

- ○ Yes
- ◉ No

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

- ☑

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

- [x] Choline chloride 50mg / Inositol 50mg / L-methionine 25mg
- [ ] Other (please describe)

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

- (•) Yes - I use it **MORE** often now (briefly describe why)
- ( ) Yes - I use it **LESS** often now (briefly describe why)
- ( ) No - use has remained consistent

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

fat metab

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

- ( ) Yes
- (•) No

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population

Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

- [x] Inositol 50mg / Choline chloride 50mg / L-methionine 25mg
- [ ] Other (please describe)

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

fat metab

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

- ◉ Yes - I use it **MORE** often now (briefly describe why)
- ○ Yes - I use it **LESS** often now (briefly describe why)
- ○ No - use has remained consistent

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

quality

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

- ○ Yes
- ◉ No

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q460.

Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

- ( ) Yes - I use it **MORE** often now (briefly describe why)
- (•) Yes - I use it **LESS** often now (briefly describe why)
- ( ) No - use has remained consistent

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

inflam

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

- ( ) Yes
- (•) No

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						

Condition 2 (please describe)

Condition 3 (please describe)

Condition 4 (please describe)

Condition 5 (please describe)

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

meyers

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

cancer

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

- Yes - I use it **MORE** often now (briefly describe why)
- (●) Yes - I use it **LESS** often now (briefly describe why)
- No - use has remained consistent

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

quality

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

- Yes
- (●) No

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender,

comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q503. Please list all combination products in which you use compounded **taurine**.

meyers

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why)
- ◉ Yes - I use it **LESS** often now (briefly describe why)
- ○ No - use has remained consistent

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

quality

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

- ○ Yes
- ◉ No

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- ☑ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)

- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [x] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [ ] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [ ] Reduced l-glutathione
- [ ] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

Neuropathy

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

Congestive heart failure

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

Depression at times

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ]

- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [x] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [ ] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

varies depending on individual patient circumstances

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

varies depending on individual patient circumstances

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

varies depending on individual patient circumstances

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

varies depending on individual patient circumstances

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

yes

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

varies depending on individual patient circumstances

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [x] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [x] Other (please describe) FABNO

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

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Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [ ] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Coenzyme Q10
- [ ] Inositol
- [ ] Lysine hydrochloride
- [ ] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [ ] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): neurological						
Condition 2 (please describe): anti-aging						
Condition 3 (please describe): mood stabilizer						
Condition 4 (please describe): potent antioxidant						
Condition 5 (please describe)						

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

soooooo many !!

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

- (●) Yes - I use it **MORE** often now (briefly describe why) [needed]
- ( ) Yes - I use it **LESS** often now (briefly describe why) [ ]
- ( ) No - use has remained consistent

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

[better, muuuuuuch better !!]

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

- (●) Yes
- ( ) No

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

- [x] Physician office
- [ ] Outpatient clinic
- [ ] Emergency room
- [ ] Operating room
- [ ] Inpatient ward
- [ ] Other (please describe) [ ]

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

- [x] Purchase from a compounding pharmacy
- [ ] Purchase from an outsourcing facility
- [ ] Compound the product yourself
- [ ] Other (please describe) [ ]

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

- [x] Convenience
- [ ] Emergencies
- [ ] Other (please describe) [ ]

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [x] Naturopathic Physician
- [ ] Nephrology

- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

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The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [x] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

neuropathies, blood sugar regulation

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

mild cognitive impairment, memory concerns

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

no

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

combined with statin use, myalgias, mitochondrial disorders/dysfuncion

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

PCOS, anxiety

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

joint pain

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

yes

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Parkinson's disease	200mg	TID	nasal spray	nasal	2 months - indefinitely	all with condition
Condition 2 (please describe):						

Condition 3 (please describe)

Condition 4 (please describe)

Condition 5 (please describe)

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

neurological conditions, environmental illness, liver disease

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

yes

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

- ( ) Yes - I use it **MORE** often now (briefly describe why)
- ( ) Yes - I use it **LESS** often now (briefly describe why)
- (•) No - use has remained consistent

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

because I can obtain it in a specific dose and form that I want for my patient

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

- ○ Yes
- ◉ No

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☑ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

blood sugar management, diabetic retinopathy, macular degeneration, heart failure

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [x] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [x] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [x] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

Diabetic neuropathy

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.

Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

Prenatal support

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

Yes

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

CHF, statin treatment

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

Yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

Anxiety

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

Herpes simplex

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

Yes

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

Joint pain

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

Yes

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

Asthma, bronchiectasis, COPD

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

Yes

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

Psychotropic medication discontinuation

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

Yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [x] Naturopathic Physician
- [ ] Nephrology
- [ ]

- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [ ] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [ ] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [ ] Reduced l-glutathione
- [ ] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [ ] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [ ]

Compounded drug product

- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

Diabetes, Fatigue, CHF, Cancer

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Yes

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

Fatigue, CHF, Kidney failure, Tinnitus, Mitochondrial dysfunction, Cancer

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

Yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

Anxiety, Depression, OCD, Agoraphobia, Bi-Polar disorder, Infertiltiy issues

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

Arthritis

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

Yes

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.

Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

Liver disorders, behavioral problems, Detoxification

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

Yes

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

Heart problems, Cardiac arrhythmias, Seizure disorders

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

Yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)

- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [x] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [x] Naturopathic Doctor
- [x] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [ ] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [x] Lysine hydrochloride
- [ ] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age,

gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Weak Chelation; Blood Sugar Stability; Anti-Oxidant; Diabetic Neuropathy	100-300 mg	1-3 IV qWeekly		IV	30-60 minutes	
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

DM & Diabetic Neuropathy

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Yes

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

- (●) Yes - I use it **MORE** often now (briefly describe why) [ ]
- ( ) Yes - I use it **LESS** often now (briefly describe why) [ ]
- ( ) No - use has remained consistent

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

Patients have reported sensitivity to the non-compounded products previously.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

- ( ) Yes
- (●) No

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

CHF and General CV Health

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

Yes

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of

therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

Anxiety and General Thyroid Support

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Viral infections as part of an immune support infusion.	100 mg	1-3 IV qWeekly		IV	1-2 hours	
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

Immune Supportive IV infusions (especially with viral infections)

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are ten (10) substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? (check all that apply)

- [x] Alpha lipoic acid (ALA)
- [ ] Choline chloride
- [x] Citrulline
- [x] Coenzyme Q10
- [x] Inositol
- [x] Lysine hydrochloride
- [x] Methylsulfonylmethane (MSM)
- [ ] Ornithine hydrochloride
- [x] Reduced l-glutathione
- [x] Taurine
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [x]

Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA)**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

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Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

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Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

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Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine hydrochloride.**

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine hydrochloride** in medical practice guidelines or other resources?

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Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine hydrochloride** changed?

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Q451. Why do you use compounded **lysine hydrochloride** instead of any FDA-approved drug product?

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Q452. Do you stock non-patient-specific compounded **lysine hydrochloride** in your practice location?

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Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine hydrochloride**? Please check all that apply.

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Q456. For which, if any, diseases or conditions do you consider **lysine hydrochloride** standard therapy?

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Q457. Does your specialty describe the use of **lysine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **methylsulfonylmethane (MSM)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **methylsulfonylmethane (MSM)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

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Q469. Why do you keep a stock of non-patient-specific compounded **methylsulfonylmethane (MSM)**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **ornithine hydrochloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **ornithine hydrochloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **ornithine hydrochloride** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **ornithine hydrochloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **ornithine hydrochloride** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **ornithine hydrochloride**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **ornithine hydrochloride** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **ornithine hydrochloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **reduced l-glutathione** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **reduced l-glutathione** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **reduced l-glutathione**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **reduced l-glutathione** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **reduced l-glutathione** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **reduced l-glutathione** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **reduced l-glutathione**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **reduced l-glutathione** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **reduced l-glutathione** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [x] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [ ] Other (please describe) _____

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [x] Citrulline
- [ ] Cupric sulfate
- [x] Inositol
- [x] Lysine
- [ ] Sodium selenite pentahydrate
- [x] Taurine
- [x] Testosterone propionate
- [x] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

Metabolic diseases

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

No

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

None - I inadvertently marked this box

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

No

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

Mouth sore prevention, metabolic diesease

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

No

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

Cystic fibrosis

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

Yes

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

Hormone supplementation or suppression

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

No

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

Wound healing, insufficient zinc levels

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

Yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [ ] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [x] Other (please describe) Pharm D

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [x] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

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If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [x] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [ ] Other (please describe) _____

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

- [ ] Compounded drug product
- [x]

- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

to sedate children for PFTs

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

no - we are trying to get away from it; but peds pulmonology has their baseline data with this drug - so it has only a restricted use

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)

- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [x] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ] Urology
- [ ] Other (please describe)

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [x] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [ ] Other (please describe) _____

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

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Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [x] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [x] Other (please describe) Pediatric anesthesiology

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [x] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [x] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [x] Other (please describe) Hospice & Palliaitive Medicine

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [x] Other (please describe) Pediatric Anesthesiology

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [x] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

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Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

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Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

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Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

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Q405. Please list all combination products in which you use compounded **citrulline**.

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Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

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Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

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Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

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Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

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Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

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This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

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Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

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Q419. Please list all combination products in which you use compounded **cupric sulfate**.

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Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

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Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

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Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

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Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

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Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

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Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

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Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

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Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

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Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [ ] Other (please describe) _____

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [x] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [x] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

Inborn error of metabolism

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

no

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product

- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Parenteral Nutrition	1 mg/ml	daily	injection	Infusion	days	neonates
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

Trace Elements, Selenium

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [x] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe) _____

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [x] Anesthesiology
- [ ] Cardiovascular Disease
- [ ] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [ ] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe) _____
- [ ] Urology
- [x] Other (please describe) Pediatric Anesthesiology

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

- [x] Compounded drug product

- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [x] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [x] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

- [x] Compounded drug product
- [x] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						

Condition 5 (please describe)

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

yes

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

- ( ) Yes - I use it **MORE** often now (briefly describe why)
- ( ) Yes - I use it **LESS** often now (briefly describe why)
- (•) No - use has remained consistent

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

we use fda approved powder and make it into a liquid

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

- (•) Yes
- ( ) No

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.

Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [ ] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [x] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

This question was not displayed to the respondent.

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

This question was not displayed to the respondent.

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [x] Unsure

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

Nutritional supplement for IV infusion with TPN

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

Yes

Q16. What is your terminal clinical degree? Please check all that apply.

- [x] Doctor of Medicine (MD)
- [ ] Doctor of Osteopathic Medicine (DO)
- [ ] Doctor of Medicine in Dentistry (DMD/DDS)
- [ ] Naturopathic Doctor (ND)
- [ ] Nurse Practitioner (NP)
- [ ] Physician Assistant (PA)
- [ ] Other (please describe)

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

- [ ] No Board certification
- [ ] Allergy and Immunology
- [ ] Anesthesiology
- [ ] Cardiovascular Disease
- [x] Critical Care Medicine
- [ ] Dermatology
- [ ] Emergency Medicine
- [ ] Endocrinology, Diabetes and Metabolism
- [ ] Family Medicine
- [ ] Gastroenterology
- [ ] Hematology
- [ ] Infectious Disease
- [ ] Internal Medicine
- [ ] Medical Toxicology
- [ ] Naturopathic Doctor
- [ ] Naturopathic Physician
- [ ] Nephrology
- [ ] Neurology
- [ ] Obstetrics and Gynecology
- [ ] Oncology
- [ ] Ophthalmology
- [ ] Otolaryngology
- [ ] Pain Medicine
- [x] Pediatrics
- [ ] Psychiatry
- [ ] Rheumatology
- [ ] Sleep Medicine
- [ ] Surgery (please describe)
- [ ]

Urology

- [x] Other (please describe) Clinical Pharmacology

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Chloral hydrate
- [ ] Choline chloride
- [ ] Citrulline
- [ ] Cupric sulfate
- [ ] Inositol
- [ ] Lysine
- [ ] Sodium selenite pentahydrate
- [ ] Taurine
- [ ] Testosterone propionate
- [ ] Zinc sulfate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **chloral hydrate**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **chloral hydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Pediatric Pulmonary Function testing	5 mg/ml	repeat once in 30 minutes	oral solution	PO	60-120 minutes	Children
Condition 2 (please describe):						
Condition 3 (please describe):						
Condition 4 (please describe):						
Condition 5 (please describe):						

Q4.
Do you use compounded **chloral hydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [ ] Combination

Q5. Please list all combination products in which you use compounded **chloral hydrate**.

This question was not displayed to the respondent.

Q6. For which, if any, diseases or conditions do you consider compounded **chloral hydrate** standard therapy?

Q7. Does your specialty describe the use of compounded **chloral hydrate** in medical practice guidelines or other resources?

Yes

Q8. Over the past 5 years, has the frequency in which you have used compounded **chloral hydrate** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) [ ]
- ○ Yes - I use it **LESS** often now (briefly describe why) [ ]
- ◉ No - use has remained consistent

Q9. Why do you use compounded **chloral hydrate** instead of any FDA-approved drug product?

One of the options

Q10. Do you stock non-patient-specific compounded **chloral hydrate** in your practice location?

- ○ Yes
- ◉ No

Q11. In what practice location(s) do you stock non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **chloral hydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **chloral hydrate** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **chloral hydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q389. Please list any conditions or diseases for which you use compounded **choline chloride** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration,

duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **choline chloride** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. In which combination(s) do you use compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **choline chloride** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **choline chloride** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **choline chloride** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **choline chloride**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **choline chloride** standard therapy?

This question was not displayed to the respondent.

Q401. Does your specialty describe the use of **choline chloride** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q403. Please list any conditions or diseases for which you use compounded **citrulline** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **citrulline** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **citrulline**.

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **citrulline** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **citrulline** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **citrulline** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **citrulline** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **citrulline**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **citrulline** standard therapy?

This question was not displayed to the respondent.

Q415. Does your specialty describe the use of **citrulline** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q417. Please list any conditions or diseases for which you use compounded **cupric sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q418.
Do you use compounded **cupric sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q419. Please list all combination products in which you use compounded **cupric sulfate**.

This question was not displayed to the respondent.

Q420. For which, if any, diseases or conditions do you consider compounded **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q421. Does your specialty describe the use of compounded **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q422. Over the past 5 years, has the frequency in which you have used compounded **cupric sulfate** changed?

This question was not displayed to the respondent.

Q423. Why do you use compounded **cupric sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q424. Do you stock non-patient-specific compounded **cupric sulfate** in your practice location?

This question was not displayed to the respondent.

Q425. In what practice location(s) do you stock non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **cupric sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **cupric sulfate** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **cupric sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q431. Please list any conditions or diseases for which you use compounded **inositol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **inositol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. In which combination(s) do you use compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **inositol** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **inositol** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **inositol** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **inositol** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **inositol**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **inositol** standard therapy?

This question was not displayed to the respondent.

Q443. Does your specialty describe the use of **inositol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q445. Please list any conditions or diseases for which you use compounded **lysine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.

Do you use compounded **lysine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. Please list all combination products in which you use compounded **lysine**.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **lysine** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **lysine** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **lysine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **lysine** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **lysine**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **lysine** standard therapy?

This question was not displayed to the respondent.

Q457. Does your specialty describe the use of **lysine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **sodium selenite pentahydrate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **sodium selenite pentahydrate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **sodium selenite pentahydrate**.

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **sodium selenite pentahydrate** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **sodium selenite pentahydrate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **sodium selenite pentahydrate** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **sodium selenite pentahydrate**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **sodium selenite pentahydrate** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **sodium selenite pentahydrate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **taurine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.
Do you use compounded **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. Please list all combination products in which you use compounded **taurine**.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **taurine** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **taurine** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **taurine** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **taurine** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **taurine**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **taurine** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **taurine** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q487. Please list any conditions or diseases for which you use compounded **testosterone propionate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **testosterone propionate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **testosterone propionate**.

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **testosterone propionate** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **testosterone propionate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **testosterone propionate** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **testosterone propionate**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **testosterone propionate** standard therapy?

This question was not displayed to the respondent.

Q499. Does your specialty describe the use of **testosterone propionate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **zinc sulfate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **zinc sulfate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **zinc sulfate**.

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **zinc sulfate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **zinc sulfate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **zinc sulfate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **zinc sulfate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **zinc sulfate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **zinc sulfate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Tab 4

Oxitriptan

Tab 4a

FDA Evaluation of Oxitriptan

DATE: May 7, 2021

FROM: Madeline Wolfert, M.D.
Physician, Pharmacy Compounding Review Team (PCRT),
Office of Specialty Medicine (OSM), Office of New Drugs (OND)

Lolita Lopez, M.D.
Lead Physician, PCRT, OSM, OND

Elizabeth Hankla, Pharm.D.
Consumer Safety Officer, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Scientific Advisor (acting), Office of New Drug Products (ONDP),
Office of Pharmaceutical Quality (OPQ)

Daiva Shetty, M.D.
Associate Director, PCRT, OSM, OND

Charles Ganley, M.D.
Director, OSM, OND

Frances Gail Bormel, R.Ph., J.D.
Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Oxitriptan (5-hydroxytryptophan (5-HTP)) for Inclusion on the 503A Bulks List - Addendum to Food and Drug Administration May 18, 2015 Review

I. INTRODUCTION AND BACKGROUND

This evaluation considers whether to include oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), known as the 503A Bulks List, for the treatment of the rare disease, tetrahydrobiopterin (BH4) deficiency.[1]

Oxitriptan was nominated and evaluated for inclusion on the 503A Bulks List for use in the treatment of insomnia and depression, not BH4 deficiency. In June 2015, FDA convened the Pharmacy Compounding Advisory Committee (PCAC) to seek its advice about whether to

[1] Tetrahydrobiopterin (BH4) deficiency is a group of rare inborn errors of metabolism.

include a number of bulk drug substances, including oxitriptan, on the 503A Bulks List. Based on its review and applying the criteria identified in the Federal Register (79 FR 37747), FDA proposed to the PCAC that oxitriptan not be included on the 503A Bulks List. At the PCAC meeting on June 17, 2015, the committee voted to recommend to FDA not to include oxitriptan on the 503A Bulks List. Taking into consideration the PCAC's advice, and after consultation with the United States Pharmacopeia (USP), FDA determined that, on balance, the criteria that it considers when conducting evaluations for the 503A Bulks List weighed against inclusion of oxitriptan on the 503A Bulks List.

On December 16, 2016, FDA published a proposed rule (81 FR 91071) to not include oxitriptan on the 503A Bulks List and provided for a 90-day period to allow for comments to be submitted for FDA's consideration in finalizing the rule. In the preamble to the December 16, 2016 proposed rule, FDA stated that, on balance, the criteria weighed against the inclusion of oxitriptan on the 503A Bulks List. In particular, the Agency's evaluation of oxitriptan revealed serious safety concerns related to the use of oxitriptan for depression, a potentially life-threatening condition, in lieu of, or causing a delay in, treatment with an available approved product and the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking a compounded oxitriptan drug product. Such risks include, for example, the concomitant use of oxitriptan with antidepressant drugs, which could result in serotonin syndrome, a serious and life-threatening drug interaction (81 FR 91078).

The Agency received comments to the 2016 proposed rule, some of which related to oxitriptan. None of the comments identified treatment of BH4 deficiency as a proposed use of compounded oxitriptan drug products. On February 19, 2019, FDA published a final rule (84 FR 4696) that established the 503A Bulks List and identified four bulk drug substances, including oxitriptan, that FDA considered and did not include on the 503A Bulks List. The rule became effective on March 21, 2019.

Thereafter, FDA was contacted by several healthcare providers and caregivers of patients with BH4 deficiency who expressed to FDA that oxitriptan is an essential and standard treatment for patients with BH4 deficiency. In April 2019, a Citizen Petition was submitted to the Agency requesting that FDA "amend 21 CFR § 216.23 and add oxitriptan … to the list of substances that can be used in compounding under section 503A of the FD&C Act … and permit continued compounding of oxitriptan for patients with tetrahydrobiopterin deficiency until oxitriptan is added to the list."[2] In July 2019, in light of the information brought to the Agency's attention about the standard of care for treating patients with BH4 deficiency, FDA issued a final guidance explaining that it generally does not intend to take action for violations of sections 501(a)(2)(B), 502(f)(1), or 505 of the FD&C Act against a licensed pharmacist in a State-licensed pharmacy or a licensed physician who compounds with the bulk drug substance oxitriptan, provided certain conditions are met, including that the compounded oxitriptan-containing drug product is intended only for oral administration. Additionally, FDA announced in the guidance that it was considering whether to reevaluate the exclusion of oxitriptan from the 503A Bulks List.

[2] Citizen Petition, Docket No. FDA-2019-P-2088-0001 (filed on 4/30/2019) is available to the public at: https://www.regulations.gov/document/FDA-2019-P-2088-0001.

This evaluation revisits whether oxitriptan should be added to the 503A Bulks List. We have evaluated publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of oxitriptan for the treatment of BH4 deficiency. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor*** of placing oxitriptan for oral administration on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).[3]

II. EVALUATION CRITERIA

In FDA's 2015 Oxitriptan Evaluation, the publicly available data on the physicochemical characteristics, nonclinical assessment (summarized below), human safety (including pharmacokinetic data), effectiveness of oxitriptan for sleep disorders and depression, and historical use in compounding was evaluated.[4] The current evaluation focuses on oxitriptan for treatment of BH4 deficiency by the oral route of administration.

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

For the reasons stated in the 2015 Oxitriptan Evaluation, we conclude that "[f]rom a chemistry viewpoint, 5-HTP appears acceptable for inclusion on the 503A list because it is a relatively simple, well-characterized API, likely to be stable in solid and solution formulations into which it is likely to be compounded and unlikely to contain significant amounts of toxic impurities."

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

For the reasons stated in the 2015 Oxitriptan Evaluation, we conclude that "[t]he available nonclinical data on 5-HTP have not identified any particular safety concerns. There is no publicly available information on the carcinogenic potential of 5-HTP. There is little evidence of general toxicity and the Ames test indicates a lack of mutagenicity. Based upon the mechanism of action, concomitant use of 5-HTP with antidepressant drugs could result in serotonin syndrome."

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[3] Inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required to receive Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on the 503A Bulks List is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

[4] The 2015 Oxitriptan Evaluation is available in the Briefing Information For The June 17-18, 2015 Meeting Of The Pharmacy Compounding Advisory Committee (PCAC) at https://wayback.archive-it.org/7993/20170405230419/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf, pages 303-313.

2. Human Safety

Databases searched for information on oxitriptan in regard to Section II.B.2 of this consultation included: PubMed, ClinicalTrials.gov, the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), NIH Genetic Rare Diseases Information Center (GARD), and various online clinical references and websites.

a. Reported adverse reactions

The 2015 Oxitriptan Evaluation discussed common adverse reactions of oxitriptan such as headache and gastrointestinal effects like diarrhea, vomiting, and nausea; the risk of serotonin syndrome was also addressed. Serotonin syndrome is a clinically diagnosed condition that occurs with hyperstimulation of serotonin receptors in the body, presenting with a variety of symptoms that may include: restlessness, confusion, shivering, tachycardia, hypertension, diarrhea, muscle twitches/ rigidity, clonus, hyperthermia, seizures, loss of consciousness, or even death (Sibley et al. 2018; Boyer and Shannon 2005).

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events (AEs) involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted in July 2018 for reports listing oxitriptan as an ingredient in an AE report. A November 26, 2018 review of 196 CAERS reports concluded that the database has reports for oxitriptan that are consistent with the diagnosis of serotonin syndrome. The review also stated there is wide variability in the quality of the reports, as some provided a lot of details of the event, and others provided sparse or confusing descriptions of the events.

In March 2021, a follow-up on CAERS reports resulted in 53 reports where oxitriptan (or 5-HTP) was listed as an ingredient in an AE report since July 2018. Some reports are consistent with common adverse effects of oxitriptan as discussed above. Of the 53 CAERS reports, one additional case was identified possibly consistent with the symptoms of serotonin syndrome:

- A 35-year-old female was reported to have "serotonin syndrome." She was taking 5-HTP and PharmaGABA-250 (gamma-aminobutyric acid 250 mg, a dietary supplement), and developed tachycardia, elevated blood pressure and bilateral calf muscle cramping. Serotonin level two weeks after stopping supplements was high, 1790 ng/mL (*Note*: reference interval 0-420 ng/mL in female patients[5]). Two months later, labs revealed a serotonin level of 125 ng/mL, and she was asymptomatic and feeling "back to normal."

Most of the CAERS cases involve an oxitriptan product formulated with many other substances in the dietary supplement, or concomitant use of other products; therefore, it is not possible to determine a causal relationship between oxitriptan and the adverse event reported.

[5] Serotonin. Labcorp. https://www.labcorp.com/tests/120204/serotonin. Accessed March 29, 2021.

A recent publication (Opladen et al. 2020) reported that the most common adverse effects of oxitriptan in patients with BH4 deficiency were gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain; irritability; motor issues such as choreoathetoid, dyskinetic, or myoclonic movements; and sweating. It also stated: "Given its co-administration with L-Dopa/DC [decarboxylase] inhibitor, numerous other adverse effects were observed, but from a pathophysiologic standpoint, these are more likely to be related entirely or at least partially to L-Dopa rather than to 5-HTP treatment." Adverse symptoms more specific to oxitriptan administration reported were tachycardia, diarrhea, and anorexia (Blau et al. 2001).

b. Clinical trials assessing safety

The ClinicalTrials.gov site lists 15 studies evaluating oxitriptan; however, none were conducted in patients with BH4 deficiency. Most had no reports of results or adverse events; one trial reported non-serious adverse events such as night sweats/increased sweating, cold/flu symptoms, injury/fall, UTI.[6] No clinical trials evaluating oxitriptan conducted in patients with BH4 deficiency were located in a search of PubMed. FDA's 2015 Oxitriptan Evaluation stated that while studies evaluating the long-term side effects of oxitriptan could not be identified, safety concerns identified in the available clinical data on oxitriptan included gastrointestinal effects (anorexia, diarrhea, vomiting, and epigastric pain) and dizziness.

Due to the safety risks outlined above, specifically, serotonin syndrome associated with oxitriptan use, if FDA places oxitriptan on the 503A Bulks List, FDA intends to make safety information about the use of oxitriptan available to prescribers, pharmacists, and the public through appropriate mechanisms.

c. Availability of alternative approved therapies that may be as safe or safer

No drug product is FDA-approved to treat BH4 deficiency. The International Working Group on Neurotransmitter Related Disorders (iNTD) published in 2020 the report, "Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies," listing the following combination as first line treatment in these patients: phenylalanine (Phe) control achieved through Phe-reduced diet and/or sapropterin dihydrochloride (a synthetic BH4 analogue), in combination with L-dopa/carbidopa and oxitriptan. Alternative therapies such as selective monoamine oxidase inhibitors and selective serotonin reuptake inhibitors are considered second and third line therapies (Opladen et al. 2020). Our search did not find any information on alternative FDA-approved therapies that may be safe or safer alternatives to oxitriptan.

Conclusions: Consistent with the 2015 Oxitriptan Evaluation, we conclude that safety concerns identified for oxitriptan include gastrointestinal effects (diarrhea, vomiting, and nausea), dizziness, and risk for serotonin syndrome. In addition, in patients with BH4 deficiency, potential adverse effects of oxitriptan also include tachycardia, sweating, irritability, and motor symptoms.

[6] The clinical trials listed evaluated oxitriptan in asthma, spinal cord injuries, depression, mood, fatigue, inflammatory bowel disease, cortisol levels and satiety. NIH U.S. National Library of Medicine, www.ClinicalTrials.gov, search term "oxitriptan". Accessed April 9, 2021.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, ClinicalTrials.gov, NIH GARD, and various online clinical references and websites.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

Treatment of tetrahydrobiopterin (BH4) deficiency[7]

Oxitriptan is used to treat patients with BH4 deficiency. BH4 deficiency comprises a heterogeneous group of treatable genetic neurotransmitter disorders characterized by motor dysfunction, impaired muscle tone, movement abnormalities, intellectual disability, and seizures (Opladen et al. 2012). BH4 deficiency is estimated to affect approximately 1 in 1,000,000 individuals in the general population; the exact number of people with this condition is unknown.[8]

BH4 is an essential cofactor for multiple enzymes, including phenylalanine (Phe) hydroxylase (PAH), tyrosine hydroxylase (TH), and tryptophan hydroxylase (TPH) (see Figure 1 below). TH and TPH are key enzymes in the conversion of precursors L-dopa and oxitriptan (5-hydroxytryptophan or 5-HTP or 5-OH-Trp in Figure 1 below) to critical neurotransmitters dopamine and serotonin, respectively. Deficiency of BH4 occurs when enzymes in its biosynthesis or regeneration pathway are affected, thus resulting in a depletion of available BH4. This limits the enzymatic processes that utilize cofactor BH4, ultimately altering Phe homeostasis and biosynthesis of dopamine and serotonin (Blau et al. 2001). Disease is caused by pathogenic variants in the genes encoding the enzymes 6-pyruvoyl-tetrahydropterin synthase (PTPS), GTP cyclohydrolase I (GTPCH) and sepiapterin reductase (SR), which are involved in BH4 biosynthesis; and dihydropteridine reductase (DHPR) and pterin-4α-carbinolamine dehydratase (PCD), which are involved in BH4 regeneration (Brennenstuhl et al. 2019) (see Figure 1 below).

[7] Other names for BH4 deficiency include: Hyperphenylalaninemia caused by a defect in biopterin metabolism; Hyperphenylalaninemia, non-phenylketonuric; Hyperphenylalaninemia due to tetrahydrobiopterin deficiency; Hyperphenylalaninemia due to BH4 deficiency. Source: Tetrahydrobiopterin deficiency. NIH Genetic Rare Diseases Information Center (GARD) available at https://rarediseases.info.nih.gov/diseases/7751/tetrahydrobiopterin-deficiency. Accessed March 18, 2021.

[8] Tetrahydrobiopterin deficiency. National Organization for Rare Disorders (NORD) available at https://rarediseases.org/rare-diseases/tetrahydrobiopterin-deficiency/. Accessed May 3, 2021.

Figure 1: Biosynthesis, regeneration and functions of tetrahydrobiopterin (Dudesek et al. 2001)

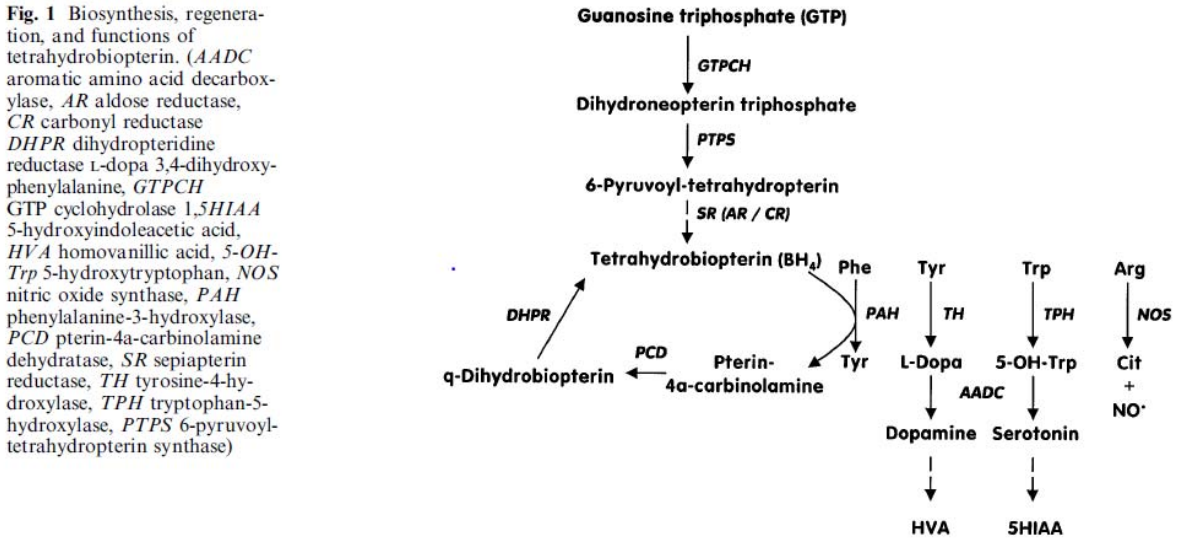

Fig. 1 Biosynthesis, regeneration, and functions of tetrahydrobiopterin. (*AADC* aromatic amino acid decarboxylase, *AR* aldose reductase, *CR* carbonyl reductase *DHPR* dihydropteridine reductase L-dopa 3,4-dihydroxyphenylalanine, *GTPCH* GTP cyclohydrolase 1,*5HIAA* 5-hydroxyindoleacetic acid, *HVA* homovanillic acid, *5-OH-Trp* 5-hydroxytryptophan, *NOS* nitric oxide synthase, *PAH* phenylalanine-3-hydroxylase, *PCD* pterin-4a-carbinolamine dehydratase, *SR* sepiapterin reductase, *TH* tyrosine-4-hydroxylase, *TPH* tryptophan-5-hydroxylase, *PTPS* 6-pyruvoyl-tetrahydropterin synthase)

BH4 deficiency typically manifests with hyperphenylalaninemia (HPA) and deficiency of the neurotransmitter precursors, L-dopa and oxitriptan. Diagnosis is usually made based on elevated Phe levels detected on the neonatal phenylketonuria (PKU) screen, and work-up includes analysis of blood and urine, cerebrospinal fluid, and gene sequencing (Opladen et al. 2020).

Symptoms of BH4 deficiency typically present in infancy, such as in the first few weeks of life with poor suck and decreased spontaneous movements, but are often noted around four months of age. Common symptoms with severe forms of BH4 deficiency are intellectual disability, impaired motor development, epileptic seizures, disturbance of tone and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infections, hypersalivation, and swallowing difficulties. Milder forms may manifest with hypotonia or transient behavioral abnormalities (Blau et al. 2001).

Treatment strategy described in the literature is two-pronged: limit HPA through restricted Phe diet and/or BH4 replacement, and substitute depleted neurotransmitters with oral precursors oxitriptan and L-dopa/carbidopa (Blau and van Spronsen 2014). Treatment should be initiated as early as possible to optimize neurodevelopmental outcome and improve/prevent worsening of symptoms (Opladen et al. 2012). Late detection and late initiation of effective treatment lead to irreversible brain damage, although some patients may have progression of disease despite treatment (Blau and van Spronsen 2014). Patients with BH4 deficiency require lifelong follow-up, and pediatric patients require frequent visits due to dosing titration and adjustments with weight gain (Opladen et al. 2020). Published literature documents orally administered oxitriptan as part of standard therapy for patients with BH4 deficiency; our search did not find any information on the use of oxitriptan by other routes of administration.

According to published medical literature, when using oxitriptan for BH4 deficiency treatment, the recommended starting dose is 1 to 2 mg/kg/day, divided in 3 to 6 doses/day, with slow titration recommended (1 to 2 mg/kg/day per week), depending on clinical response and side

effects. Measurement of neurotransmitter metabolites in cerebrospinal fluid may also be helpful in dose titration. Recommended target dose is variable (Opladen et al. 2020). Bramwell (2011) cites recommended pediatric dose 4 to 10 mg/kg/day divided 3 to 4 times/day. In one study, 5-HTP was initiated at 1 mg/kg/day, then increased every 2 to 5 days in 1 mg increments to a target dosage of 5 mg/kg/day (Liu et al. 2008). Individual dosing adjustment may be indicated based on clinical response and side effects (Opladen et al. 2020).

The International Working Group on Neurotransmitter Related Disorders (iNTD)

The iNTD consensus guideline recommends (categorized as a strong recommendation) that from a biochemical standpoint, oxitriptan is considered a first-line treatment in BH4 deficiency as benefits clearly outweigh adverse effects.[9] Improvement in developmental progression, cognition, tone and movement disorders, seizures, swallowing difficulty and hypersalivation, speech development, attention and behavior, and mood were observed with oxitriptan treatment. However, evidence of direct effect of oxitriptan is limited by concurrent treatment with L-dopa/carbidopa and/or sapropterin dihydrochloride/ Phe-reduced diet. In some cases, oxitriptan treatment failed to improve symptoms, as with L-dopa/carbidopa (Opladen et al. 2020).

Case reports on treatment of tetrahydrobiopterin (BH4) deficiency with oxitriptan

Numerous case reports worldwide regarding treatment for BH4 deficiency with oxitriptan have been published. These include:

- A 10 kg child with HPA with normal phenylalanine hydroxylase activity (initially diagnosed as PKU and treated with Phe-restricted diet) showed steady improvement in myoclonus, uncontrolled movements, hypersalivation, and head control when treated with oxitriptan (40 mg) and L-dopa (Bartholome 1974; Bartholome and Byrd 1975).
- Long-term follow up of patients with 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency described 5 cases (Dudesek et al. 2001):
    - Case 1 and 3: neurotransmitter substitution with oxitriptan and L-dopa/carbidopa ultimately failed to improve clinical condition (patients were treated with 2.3 mg/kg/day oxitriptan and 1.6 mg/kg/day titrated up to 11.9 mg/kg/day of oxitriptan, respectively).
    - Case 2: treatment with L-dopa/carbidopa and 1.5 mg/kg/day oxitriptan for 5 weeks abolished symptoms of limb rigidity and foot clonus; patient was ultimately maintained on BH4 monotherapy with stable clinical status.
    - Case 4: mild phenotype with normal infant development, successfully treated with Phe-restricted diet and BH4 monotherapy, which was weaned at 5 years old.
    - Case 5: hypotonia, swallowing difficulties, seizures improved with increased doses of L-dopa/carbidopa and oxitriptan. The child was started on 1 mg/kg/day of oxitriptan at 5 months, that was carefully titrated to 1.9 mg/kg/day. Doses were increased at 6 months (oxitriptan increased to 3.4 mg/kg/day) due to swallowing difficulties and extension seizures, with marked improvement in clinical status. L-dopa/carbidopa and oxitriptan doses were increased stepwise with age, with dose range of oxitriptan between 3.6 to 4.3 mg/kg/day.
- A 27-month-old child with dihydropteridine reductase (DHPR) deficiency presented with reported global developmental delay, hypotonia, and seizures despite treatment with a

[9] For PCD and autosomal dominant GTPCH deficiencies, no recommendation was given due to lack of evidence.

Phe-restricted diet, folinic acid, and L-dopa since initial diagnosis. L-dopa was switched to carbidopa/levodopa, and oxitriptan (2 mg/kg/day, administered four times daily) and sapropterin dihydrochloride were added. She improved developmentally in areas of receptive language and motor strength, in addition to increased alertness and responsiveness. It is unclear whether clinical improvement was attributable to BH4 supplementation, or initiation of L-dopa/carbidopa and oxitriptan (Coughlin et al. 2012).

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Range of symptomatology of BH4 deficiency is discussed above. Untreated patients demonstrate severe cerebral deterioration and many of them die at an early age, which is why the term "malignant HPA" was suggested when BH4 deficiency was initially being described (Blau et al. 2001). Treatment of BH4 deficiency is focused on managing the symptoms and preventing long-term nervous system damage.[10]

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

Oral oxitriptan in combination with other treatment is standard first line therapy for BH4 deficiency. This combination therapy includes Phe control through diet and/or synthetic tetrahydrobiopterin (sapropterin dihydrochloride); and amine neurotransmitter precursors, oxitriptan and L-dopa. No drug product is FDA-approved to treat BH4 deficiency. The 2020 iNTD consensus guideline notes that if used as monotherapy, sapropterin dihydrochloride [an active pharmaceutical ingredient in an FDA-approved product] has been reported in several cases to fail to improve or prevent intellectual disability, movement disorders, seizures or sleep problems. Alternative therapies such as selective monoamine oxidase inhibitors and selective serotonin reuptake inhibitors are considered second and third line therapies, with limited evidence of effectiveness available (Opladen et al. 2020). Our search did not find any additional information on alternative FDA-approved therapies that may be more effective or as effective alternatives to oxitriptan.

Conclusions: Administration of oral oxitriptan is considered a first-line treatment in BH4 deficiency in combination with other therapy. Clinical information suggests therapeutic potential in patients with BH4 deficiency when used in combination with other first line treatment. Limitations in the data include concomitant administration of other first-line therapies and lack of controlled clinical trials.

D. Has the substance been used historically in compounding?

Databases searched for information on oxitriptan in regard to Section II.D. of this consultation included PubMed, Natural Medicines, European Pharmacopoeia, Japanese Pharmacopoeia, CompoundingToday.com, and Google.

[10] Tetrahydrobiopterin deficiency. NIH Genetic Rare Diseases Information Center (GARD) available at https://rarediseases.info.nih.gov/diseases/7751/tetrahydrobiopterin-deficiency. Accessed March 18, 2021.

1. *Length of time the substance has been used in pharmacy compounding*

Based on published literature, oxitriptan has been used in pharmacy compounding since at least 2011 (Bramwell 2011); but it can be presumed that it has been used since about 1975 when dosing in children was first described for BH4 deficiency (Bartholome and Byrd 1975).[11]

2. *The medical condition(s) it has been used to treat*

According to the Natural Medicines Database, oxitriptan is used for sleep disorders, depression, anxiety, migraine and tension-type headaches, fibromyalgia, obesity, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), attention deficit-hyperactive disorder (ADHD), cerebellar ataxia, obsessive-compulsive disorder (OCD), opioid withdrawal, Ramsey-Hunt syndrome, Down syndrome, insomnia, and as adjunctive therapy in seizure disorders, schizophrenia, and Parkinson disease (Natural Medicines Comprehensive Database, 2021). It is unknown whether oxitriptan is typically compounded into a drug product when used for the conditions above or whether, for example, a dietary supplement of oxitriptan is typically used.

There is evidence that oxitriptan has been used in pharmacy compounding for BH4 deficiency based on the following:

- After FDA issued a final rule on February 19, 2019, where FDA did not place oxitriptan on the 503A Bulks List, we received several communications from pharmacists and caregivers regarding the use of oxitriptan to treat patients with BH4 deficiency. According to those communications, oxitriptan is the standard of care for the treatment of BH4 deficiency.[12]
- The International Journal of Pharmaceutical Compounding (IJPC) published a compounding formula for an oxitriptan 3 mg/5 mL oral liquid in almond oil for treating BH4 deficiency (Bramwell 2011). According to the author, "Treatment for children with PKU is lifelong dietary Phe [phenylalanine] restriction and, for those with BH4 deficiency, treatment also includes tetrahydrobiopterin, carbidopa/levodopa, and 5-hydroxytryptophan (5-HTP)." In addition, the author states that the "Recommended pediatric dose [of oxitriptan] is 4 to 10 mg/kg/day PO [oral administration] divided tid-qid [three times a day to four times a day] with an optimal dose of 6 to 8 mg/kg/day."

No publications were located when PubMed was searched for any mention of human compounding and oxitriptan, 5-HTP, 5-hydroxytryptophan, or BH4.

A search of CompoundingToday.com by the International Journal of Pharmaceutical Compounding yielded two compounding formulas that contain oxitriptan as a single ingredient: a 300 mg gelatin troche[13] and a 2 mg/5 mL oral suspension in almond oil.[14] While these

[11] BH4 deficiency was first described in the scientific literature as a "PKU variant", "atypical PKU" or "malignant PKU."

[12] See guidance entitled, Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/compliance-policy-certain-compounding-oral-oxitriptan-5-htp-drug-products-patients for additional information.

[13] See https://compoundingtoday.com/Formulation/NamedSearchByKeyword.cfm.

[14] See https://compoundingtoday.com/Formulation/SearchByKeyword.cfm.

formulas do not include information on the medical condition the product is intended to treat, the oral suspension formula page categorizes the product as an "AntiDepressant, Nutritional Biologically Active, [and] Nutritional Oral" and includes a "use" section which states, "5-Hydroxytriptophan [5-hydroxytryptophan], 5-HTP, is an aromatic amine and immediate precursor of serotonin. 5-HTP readily crosses the blood brain barrier, increasing CNS synthesis of serotonin. Recommended pediatric dose is 4 to 10-mg/Kg/day orally divided into 3 to 4 doses per day. The optimal dose is considered to be 6 to 8-mg/Kg/day." When using oxitriptan for BH4 deficiency, dosing is typically started at 1-2 mg/kg/day in divided doses and titrated based on clinical response and side effects (Opladen et al. 2020).

3. *How widespread its use has been*

Insufficient data are available from which to draw conclusions about the extent of use of oxitriptan in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

A search of the European Pharmacopoeia (10th Edition 10.3), and the Japanese Pharmacopoeia (17th Edition, Supplement II) did not show any monograph listings for oxitriptan or 5-HTP. Our search did not find evidence to confirm that oxitriptan is a component of an approved drug product in other countries.

Conclusions: Oxitriptan has been used in pharmacy compounding since at least 2011 for treating BH4 deficiency.

III. RECOMMENDATION

We have balanced the criteria described in Section II above to evaluate oxitriptan for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor*** of oxitriptan for oral administration being placed on that list based on the following:

1. Oxitriptan is well-characterized physically and chemically.

2. Available nonclinical data on oxitriptan have not identified particular safety concerns. Regarding safety in humans, adverse effects associated with the use of oxitriptan include gastrointestinal symptoms (such as diarrhea, vomiting, and nausea), sweating, tachycardia, motor symptoms, and risk of serotonin syndrome.

3. Administration of oral oxitriptan in combination with other treatments is considered a first-line treatment in BH4 deficiency. No drug product is FDA-approved to treat BH4 deficiency. Clinical information suggests therapeutic potential in patients with BH4 deficiency when used in combination with other first line treatment. Limitations in the data include concomitant administration with L-dopa/carbidopa and BH4 replacement, and lack of controlled clinical trials.

4. Oxitriptan has been documented in pharmacy compounding since at least 2011 for treating BH4 deficiency, although presumably used since the 1970s when treatment in children was described in the literature.

We have revisited whether oxitriptan should be added to the 503A Bulks List, addressing the use of compounded oxitriptan for BH4 deficiency, the careful monitoring of dose and side effects in this population of patients, and the lack of alternative treatment. Based on this information the Agency has considered, a balancing of the evaluation criteria weighs in favor of oxitriptan for oral administration being added to the 503A Bulks List.

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APPENDIX 1: FDA Review of Oxitriptan for Inclusion on the 503A Bulk Substances List (May 2015)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: May 18, 2015

FROM:

Glenn Mannheim, M.D.
Medical Officer
Division of Psychiatry Products (DPP)

Jerry M. Cott, Ph.D.
Pharmacology Toxicology Reviewer
Division of Psychiatry Products (DPP)

Praveen Balimane, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology I (DCP I)

Courtney Suggs, Pharm.D., MPH
Reviewer
Division of Pharmacovigilance I

David Claffey, Ph.D.
CMC Lead
Office of Pharmaceutical Quality

THROUGH:

Ellis Unger, M.D.
Director, Office of Drug Evaluation I

Mitchell Mathis, M.D.
Director
Division of Psychiatry Products (DPP)

Jing Zhang, MD, Ph.D.
Medical, Team Leader
Division of Psychiatry Products (DPP)

Linda Fossom, Ph.D.
Pharmacology Toxicology Team Leader
Division of Psychiatry Products (DPP)

Hao Zhu, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology I (DCP I)

Ida-Lina Diak, Pharm.D., MS
Team Leader
Division of Pharmacovigilance I

Ramesh Sood, Ph.D.
Senior Scientific Advisor (Acting)
Office of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Oxitriptan for Inclusion on the 503A Bulk Drug Substances List

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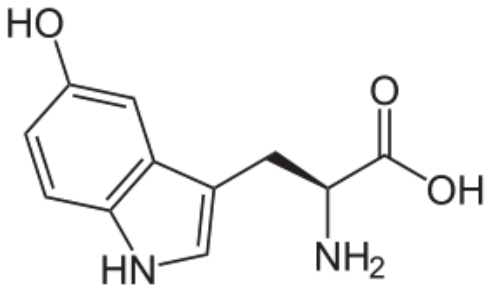
I. INTRODUCTION

Oxitriptan (5-Hydroxytryptophan (5-HTP)) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It is a naturally occurring amino acid and chemical precursor as well as a metabolic intermediate in the biosynthesis of the neurotransmitter serotonin.

The substance was nominated for use in the treatment of sleep disorders and depression[a]. The Division of Psychiatry Products (the Division) is charged with determining the safety and efficacy of psychiatric drugs, including those intended to treat sleep disorders and depression. We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use of oxitriptan. For the reasons discussed below, we recommend that oxitriptan ***not*** be added to the list of bulk drug substances that may be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?



a Oxitriptan was also nominated for use in weight loss. That indication was not considered as no support for the indication was provided.

1. Stability of the API and likely dosage forms

5-HTP is a hydroxylated form of a naturally occurring amino acid, tryptophan. It is a small molecule that can be readily characterized. It contains one stable chiral center. It is currently marketed as a dietary supplement as tablets or capsules. There were no reports found in the literature of stability issues when stored under typical room temperature conditions.

2. Probable routes of API synthesis

It is extracted from *Griffonia simplicifolia* seeds. A literature search did not find any public information on the extraction procedures used.

3. Likely impurities

5-HTP became a popular supplement after suspected toxic impurity issues associated with L-tryptophan (the precursor of L-5-HTP) arose in the 1980s (1). Although closely structurally related to tryptophan, 5-HTP's source is different (seeds vs. bacterial broth), and, therefore, the same potentially toxic impurities are unlikely to be present. Structurally, it does not appear susceptible to hydrolysis. Oxidation products, in particular 5,6-dihydroxytryptamine, were reported in the literature (2), but they do not appear to form under normal storage conditions and are unlikely to be present. Impurities from the seed extraction are likely. A *peak X* was possibly implicated in one batch associated with a single possible case of eosinophilia-myalgia syndrome (EMS) (2). Further studies (2) indicated that this peak may have been an analytical artifact.

4. Toxicity of those likely impurities

The only likely impurities are those carried over from the seed extraction. There is no indication that these impurities present significant toxicity.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Solid state properties are unlikely to affect performance due to its relatively high water solubility.

6. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize.

5-HTP is a relatively small chiral molecule. Therefore, its characterization is likely straightforward. A single (L-) isomer is likely due to its isolation from a natural source.

Conclusions: From a chemistry viewpoint, 5-HTP appears acceptable for inclusion on the 503A list because it is a relatively simple, well-characterized API, likely to be stable in solid and solution formulations into which it is likely to be compounded and unlikely to contain significant amounts of toxic impurities.

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical assessment

In addition to the specific references cited below, PubMed and ToxNet databases were consulted in the preparation of this review.

a. Pharmacology of the drug substance

5-HTP is a chemical precursor in the biosynthesis of the neurotransmitters serotonin and melatonin from tryptophan. 5-HTP crosses the blood–brain barrier and is decarboxylated to serotonin.

b. Safety pharmacology

The only published data are from a Japanese paper that includes only the abstract and tables in English (3).

L-5-HTP, the levo enantiomer of 5-HTP, produced a decrease in spontaneous locomotor activity in mice. It lowered body temperature in mice and tended to induce a drowsy EEG pattern in rabbits. L-5-HTP did not affect seizure threshold, but antagonized the behavioral changes induced by reserpine, tetrabenazine, and p-CPA by repleting serotonin in brain.

c. Acute toxicity

The only published data are from a Japanese paper that includes only the abstract and tables in English (3). Median lethal dose (LD50)'s of L-5-HTP in mg/kg are as follows:

Mice (male) p.o. 1750; i.p. 450; i.v. 375
Rats - 5-week old (male) p.o. 293; i.p. 102; (female) p.o. 478; i.p. 156.
Rats - 11-week old (male) p.o. 243; i.p. 91.

d. Repeat dose toxicity

No information available.

e. Mutagenicity

L-5-HTP was not mutagenic in *Salmonella typhimurium* TA100 at concentrations of 100-500 µg/plate without S-9 mix (4), nor did it result in any mutagenic effects in any of 5 strains of *Salmonella typhimurium* either with or without S-9 at 50 to 500 µg/plate (5).

f. Developmental and reproductive toxicity

No evidence for teratogenicity of L-5-HTP was observed in pregnant CD-1 mice when administered from 50 to 450 mg/kg in corn oil by oral gavage during organogenesis at doses that produced marginal evidence of maternal toxicity (clinical signs and trends for reduced body weights and weight gain). Fetal toxicity was limited to a highly significant dose-response trend toward decreased fetal weight, with significantly lower fetal weight in the 300 and 450 mg/kg groups relative to controls (6).

g. Carcinogenicity

No information available.

h. Toxicokinetics

No information available.

i. Other Issues

(1) In 1989 and 1990, ingestion of contaminated supplements of L-tryptophan caused eosinophilia–myalgia syndrome (EMS) in over 1500 people. Because of the differences in production methods and the lack of reports of EMS connected with 5-HTP, the risk of EMS seems remote.

(2) The 5-HTP pretreatment model has historically been used in rodents as a screen for potential therapeutic agents that have their effects via central serotonergic systems. Thus, antidepressant drugs such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, when combined with 5-HTP, may result in behavioral effects similar to serotonin syndrome.

Conclusions: The available nonclinical data on 5-HTP have not identified any particular safety concerns. There is no publicly available information on the carcinogenic potential of 5-HTP. There is little evidence of general toxicity and the Ames test indicates a lack of mutagenicity. Based upon the mechanism of action, concomitant use of 5-HTP with antidepressant drugs could result in serotonin syndrome (see conclusions under the Human Safety section, below).

2. Human Safety

a. Reported adverse reactions

Because 5-HTP has not been thoroughly studied in a clinical setting, possible side effects and interactions with other drugs are not well known. However, acute moderate gastrointestinal effects, such as diarrhea and vomiting, are common upon administration of 5-HTP, probably due to rapid formation of serotonin in the upper intestinal tract.

A Cochrane review identified nausea and gastrointestinal distress as the most notable side effects reported with 5-HTP and tryptophan (7). As stated above, a possible association of tryptophan with EMS occurred in 1989 affecting nearly 1500 tryptophan users and leading to over 30 deaths. It is still uncertain whether the tryptophan, which contained an impurity, was the cause. Tryptophan was subsequently withdrawn from the market in the United States.

The most common adverse effects in a parallel-design, 8-week study comparing 5-HTP and fluoxetine in 60 subjects with a first depressive episode were nausea, anorexia, and headache in the 5-HTP group (8).

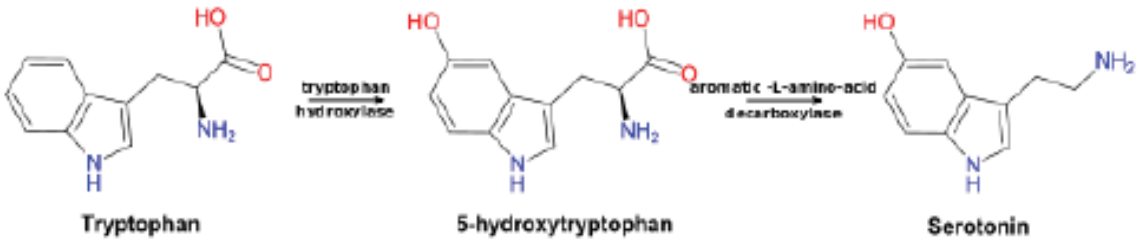
b. Clinical trials assessing safety

Common side effects identified in two, placebo-controlled trials up to 10 weeks in duration and involving 64 subjects exposed to 5-HTP or tryptophan included dizziness and epigastric pain as adverse events leading to withdrawal (7). Diarrhea was also reported but did not result in patient withdrawal. Studies evaluating the long-term side effects of 5-HTP could not be identified.

c. Pharmacokinetic data

5-HTP is known to be well-absorbed after oral dosing with an absolute bioavailability of 70%. It is absorbed rapidly, with a T_{max} of 2-3 hours and biological $T_{1/2}$ of around 6 hours. It demonstrates linear pharmacokinetics in the dose range of 50 mg to 200 mg.

The psychoactive action of 5-HTP is related to increased production of serotonin in central nervous system tissue. 5-HTP is decarboxylated to serotonin by the enzyme aromatic-L-amino-acid decarboxylase with the help of vitamin B6. This reaction occurs both in nervous tissue and in the liver.



In one study, co-administration with carbidopa (a peripheral decarboxylase inhibitor) greatly increased plasma 5-HTP levels (a 5- to15-fold increase) (9).

d. Dosage

Because this product is sold as a dietary supplement, there are no specific dosing recommendations for the treatment of depression or insomnia. Various online sources offer conflicting information. Some sites recommend an initial dosage for 5-HTP of 50 mg, three times daily with meals, followed by an increase to 100 mg, three times daily, if clinical response is inadequate after 2 weeks. Other sites recommend a starting dose of 200 mg per day, increasing to 300 to 600 mg daily for maintenance treatment. In one controlled trial, 5-HTP was started at 50 mg, three times a day, and titrated to a total daily dose of 400 mg (divided) by the fourth week of treatment (8).

For insomnia, dosage recommendations fall in the 100 to 300 mg range, to be taken before bedtime. Some sites recommend beginning with 50 mg and titrating because some patients may experience mild nausea when initiating treatment with 5-HTP.

e. The availability of alternative approved therapies that may be as safe or safer

Depression: Multiple antidepressants such as selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, escitalopram and fluvoxamine), serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine, desvenlafaxine and duloxetine), and tricyclic antidepressants (e.g., amitriptyline, desipramine, and imipramine), are currently FDA-approved, available for use in adults, meet established criteria for safety and efficacy, and are labeled accordingly.

Insomnia: Several drugs (e.g., zolpidem, eszopiclone, ramelteon, zaleplon) are FDA-approved, available for short-term use for insomnia, and meet established criteria for safety and efficacy.

Conclusions: Safety concerns identified in the available clinical data on 5-HTP include gastrointestinal effects (anorexia, diarrhea, vomiting, and epigastric pain) and dizziness. Studies evaluating the long-term side effects of 5-HTP could not be identified.

Based on mechanism of action, concomitant use of 5-HTP with antidepressant drugs could result in serotonin syndrome. Serotonin syndrome is a serious and life-threatening drug interaction caused by excess serotonin on the central and/or peripheral nervous system. Serotonin syndrome symptoms may include mental status changes, neuromuscular symptoms, seizures, and/or gastrointestinal symptoms.

Furthermore, medications used to treat depression have been linked to an increase in suicidal thinking and behavior; there are no data to suggest that 5-HTP would be free of similar risks.

C. Are there concerns about whether the substance is effective for a particular use?

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Depression: A study comparing 8 weeks of 5-HTP to 8 weeks of fluoxetine in 60 subjects (randomized 1:1) with mild, unipolar depression suggests that 5-HTP may be effective in mild, unipolar depression—a similar percentage of subjects in each arm were categorized as "responders" based on the Clinical Global Impression scale (8). A Cochrane Review identified 108 trials examining 5-HTP in the treatment of depression. Of these, only two met the authors' standards for quality and scientific rigor (7). Criteria for acceptability of studies for inclusion by the authors consisted of comparing 5-HTP to placebo, being double blind and randomized in design, and using some measure of depression as an outcome variable. These two trials were up to 10 weeks in duration and involved only 64 subjects exposed to 5-HTP or tryptophan. Although these two trials seemed to indicate that there could be some effect from 5-HTP for depression, more evidence is needed to establish efficacy. The outcomes of those trials are of limited utility for establishing effectiveness because of the small number of patients enrolled and the short-term nature of the study. Studies evaluating the long-term side effects of 5-HTP could not be identified.

Insomnia: Efficacy has not been established in controlled, double-blind trials. An open-label study suggested benefit in sleep terrors in children (10). A randomized, double-blind trial comparing a combination of gamma-aminobutyric acid (GABA) and 5-HTP to placebo in 18 subjects with insomnia (9 per group) demonstrated significantly decreased time to sleep onset and significantly increased sleep duration compared to placebo (11). However, given the small sample size, and the fact that a combination product was studied (not 5-HTP alone), this trial cannot be considered adequate for purposes of establishing evidence of efficacy for 5-HTP.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Depression can range from mild to severe and is associated with an increased risk of suicide. Failure to adequately diagnose and treat depression can have serious consequences ranging from self-harm to death. Approved antidepressants are labeled with a boxed warning to alert clinicians that suicidal ideation and behavior may occur with treatment.

3. Whether there are any alternative approved therapies that may be as effective or more effective.

As discussed in section B.2.e, above there are multiple FDA-approved therapies for the treatment of both depression and insomnia.

Conclusions:

Depression: There are limited data supporting the use of 5-HTP for the treatment of depression. Furthermore, there is no evidence to support long-term efficacy of 5-HTP for the treatment of this chronic disease. Depression is serious and potentially life-threatening and there are multiple effective FDA-approved antidepressants.
Insomnia: The clinical trials examining efficacy for insomnia were neither adequate nor well-controlled. There are multiple FDA approved drug products for the treatment of insomnia.

D. Has the substance been used historically in compounding?

1. Length of time the substance has been used in pharmacy compounding

We are uncertain of the length of time 5-HTP has been used in compounding. However, we found articles discussing its use dating back to the 1970s.

2. The medical condition(s) it has been used to treat

It has been reported that oral 5-HTP has been used for sleep disorders, depression, anxiety, migraine, tension headaches, fibromyalgia, binge eating associated with obesity, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), attention deficit hyperactive disorder (ADHD), cerebellar ataxia, Ramsey-Hunt syndrome, Down syndrome, insomnia, and as adjunctive therapy in seizure disorder and Parkinson's disease (12). It has also been reported that in combination with carbidopa, 5-HTP has been used for treating intention myoclonus and post-anoxia myoclonus (12).

3. How widespread its use has been

As discussed above, 5-HTP is marketed as a dietary supplement. A search of the Natural Medicines Comprehensive Database identified 623 products containing 5-HTP (12).

4. *Recognition of the substance in other countries or foreign pharmacopeias*

5-HTP is used in other countries; the specific countries and amount of use is uncertain.

Conclusions: Although the length of time 5-HTP has been used in compounding is uncertain, it has been discussed in scientific journals dating back approximately 40 years.

III. RECOMMENDATION

We have reviewed the physiochemical characteristics, safety, effectiveness, and historical use of 5-HTP. 5-HTP is well characterized physically and chemically. It is currently available in this country as a dietary supplement. Safety concerns associated with the use of 5-HTP, include gastrointestinal effects (anorexia, diarrhea, vomiting, and epigastric pain) and dizziness.

The efficacy of 5-HTP for the treatment of depression has not been established. Moreover, there are multiple alternative and proven FDA-approved therapies available for that indication. Depression is a serious condition and the potential consequences of failure to treat depression adequately include death. As referenced above, concomitant use of 5-HTP with antidepressant drugs could, based on mechanism of action, result in serotonin syndrome, a serious, life-threatening drug interaction. Furthermore, medications used to treat depression have been linked to an increase in suicidal thinking and behavior and there are no data to suggest that 5-HTP would be free of similar risks. Without proper labeling, neither the prescriber nor the user can be adequately warned of these risks. Although there may be some evidence of effectiveness of 5-HTP to treat insomnia., there are a number of FDA-approved products available to treat that indication.

In light of these factors, we recommend that 5-HTP ***not*** be placed on the list of bulk drug substances that can be used in compounding.

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APPENDIX 2: Proposed Rule: List Of Bulk Drug Substances That Can Be Used To Compound Drug Products In Accordance With Section 503A Of The Federal Food, Drug, and Cosmetic Act (December 2016)

Report SE–623, Issue 16''). Accomplishing the revision required by this paragraph terminates the requirements of paragraph (g) of this AD. Accomplishing the revision required by this paragraph also terminates the requirements of paragraph (g) of AD 2012–12–07.

(1) The initial compliance times for the tasks specified in Fokker Services B.V. Engineering Report SE–623, Issue 16, are at the later of the applicable compliance times specified in Fokker Services B.V. Engineering Report SE–623, Issue 16, or within 30 days after the effective date of this AD, whichever is later.

(2) If any discrepancy is found, before further flight, repair using a method approved by the Manager, International Branch, ANM–116, Transport Airplane Directorate, FAA; or the EASA; or Fokker B.V. Service's EASA DOA.

(l) No Alternative Actions or Intervals

After the maintenance or inspection program, as applicable, has been revised as required by paragraph (k) of this AD, no alternative actions (*e.g.,* inspections) or intervals may be used unless the actions or intervals are approved as an AMOC in accordance with the procedures specified in paragraph (m)(1) of this AD.

(m) Other FAA AD Provisions

The following provisions also apply to this AD:

(1) *Alternative Methods of Compliance (AMOCs):* The Manager, International Branch, ANM–116, Transport Airplane Directorate, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or local Flight Standards District Office, as appropriate. If sending information directly to the International Branch, send it to ATTN: Tom Rodriguez, Aerospace Engineer, International Branch, ANM–116, Transport Airplane Directorate, FAA, 1601 Lind Avenue SW., Renton, WA 98057–3356; telephone 425–227–1137; fax 425–227–1149. Information may be emailed to: *9-ANM-116-AMOC-REQUESTS@faa.gov.* Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the local flight standards district office/certificate holding district office.

(2) *Contacting the Manufacturer:* As of the effective date of this AD, for any requirement in this AD to obtain corrective actions from a manufacturer, the action must be accomplished using a method approved by the Manager, International Branch, ANM–116, Transport Airplane Directorate, FAA; or EASA; or Fokker B.V. Services' EASA DOA. If approved by the DOA, the approval must include the DOA-authorized signature.

(n) Related Information

(1) Refer to Mandatory Continuing Airworthiness Information (MCAI) EASA AD 2016–0125, dated June 21, 2016, for related information. You may examine the MCAI on the Internet at *http://www.regulations.gov* by searching for and locating Docket No. FAA–2016–9435.

(2) For service information identified in this AD, contact Fokker Services B.V., Technical Services Dept., P.O. Box 1357, 2130 EL Hoofddorp, the Netherlands; telephone: +31 (0)88–6280–350; fax: +31 (0)88–6280–111; email: *technicalservices@fokker.com;* Internet *http://www.myfokkerfleet.com.* You may view this service information at the FAA, Transport Airplane Directorate, 1601 Lind Avenue SW., Renton, WA. For information on the availability of this material at the FAA, call 425–227–1221.

Issued in Renton, Washington, on November 17, 2016.

Phil Forde,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 2016–28669 Filed 12–15–16; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA–2016–N–3464]

RIN 0910–AH29

List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing a regulation to identify an initial list of bulk drug substances that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. Specifically, the Agency proposes to place six bulk drug substances on the list. This proposed rule also identifies four bulk drug substances that FDA has considered and proposes not to include on the list. Additional substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of a future rulemaking.

DATES: Submit either electronic or written comments on the bulk drug substances list by March 16, 2017. See section VI for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *http://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *http://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2016–N–3464 for ''List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *http://www.regulations.gov* or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *http://www.regulations.gov.* Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *http://www.fda.gov/regulatoryinformation/dockets/default.htm.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: James Flahive, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5108, Silver Spring, MD 20993–0002, 301–796–9293.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend its regulations to add a list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as ''the 503A Bulks List''). Bulk drug substances that appear on the 503A Bulks List can be used to compound drug products subject to the conditions of section 503A, although those substances are not the subject of a USP or NF monograph or components of approved drug products.

B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to establish the criteria by which bulk drug substances will be evaluated for inclusion on the 503A Bulks List. Based on the results of its evaluation of nominated bulk drug substances to date, as well as consultation with the Pharmacy Compounding Advisory Committee (PCAC), FDA is also proposing to include six bulk drug substances on the list: Brilliant Blue G, also known as Coomassie Brilliant Blue G–250; cantharidin (for topical use only); diphenylcyclopropenone (for topical use only); N-acetyl-D-glucosamine (for topical use only); squaric acid dibutyl ester (for topical use only); and thymol iodide (for topical use only) and that four other substances not be included on the list: Oxitriptan, piracetam, silver protein mild, and tranilast.

C. Legal Authority

Section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serves as our principal legal authority for this proposed rule.

D. Costs and Benefits

FDA is proposing to place six bulk substances on the 503A Bulks List and not to place four bulk substances on the 503A Bulks List. Because we lack sufficient information to quantify the costs and benefits of this proposed rule, we include a qualitative description of potential benefits and potential costs. We expect that the rule would affect compounding pharmacies and other entities that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected drug substances, and payers that cover these drug products or alternative drug products.

II. Table of Abbreviations and Acronyms Commonly Used in This Document

5-HTP 5-hydroxytryptophan
BLA Biologics License Application
CFR Code of Federal Regulations
CSA Controlled Substances Act
DPCP Diphenylcyclopropenone
DQSA Drug Quality and Security Act
FD&C Act Federal Food, Drug, and Cosmetic Act
FDA Food and Drug Administration
IND Investigational New Drug
NAG N-acetyl-D-glucosamine
NAICS North American Industry Classification System
NF National Formulary
NPRM Notice of Proposed Rulemaking
OTC Over-The-Counter
PCAC Pharmacy Compounding Advisory Committee
PHS Act Public Health Service Act
PRESTO Prevention of REStenosis with Tranilast and its Outcomes
RFA Regulatory Flexibility Analysis
SADBE Squaric acid dibutyl ester
SBA Small Business Administration
UGT1A1 Uridine diphosphate glucuronosyltransferase 1A1
UK United Kingdom
USP United States Pharmacopeia

III. Background

A. Statutory and Regulatory Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a compounded drug product may qualify for an exemption from certain sections of the FD&C Act. Those conditions include that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) Comply with the standards of an applicable USP or NF monograph,[1] if a

[1] FDA has interpreted the statutory language ''applicable USP or NF monographs'' to refer to official USP or NF drug substance monographs. Therefore, a substance that is the subject of a dietary supplement monograph, but not a USP or NF drug substance monograph, does not satisfy the

monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on the 503A Bulks List. See section 503A(b)(1)(A)(i) of the FD&C Act. This proposed rule proposes criteria for evaluating substances for inclusion on the 503A Bulks List and identifies six substances the Secretary proposes to place on the list. The Agency considered four other substances and is proposing not to include those substances on the 503A Bulks List. Additional substances are under evaluation, and new substances may be added to the list through subsequent rulemaking.

Section 503A adopts the definition of ''bulk drug substance'' in FDA's drug establishment registration and listing regulations, which was codified at § 207.3(a)(4) (21 CFR 207.3(a)(4)) at the time section 503A was enacted. See section 503A(b)(1)(A) of the FD&C Act. Under the definition, bulk drug substance means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

On August 31, 2016, FDA published a final rule in the **Federal Register** to update its registration and listing regulations in part 207 (21 CFR part 207), which included minor changes to the definition of bulk drug substance and moved the definition to § 207.3 (see 81 FR 60170). This definition becomes effective on November 29, 2016. As set forth in § 207.3, ''bulk drug substance,'' as referenced in section 503A(b)(1)(A) of the FD&C Act, means the same as ''active pharmaceutical ingredient'' as defined in § 207.1(b). An ''active pharmaceutical ingredient'' is any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance (§ 207.1).

Inactive ingredients used in compounded drug products, such as flavorings, dyes, or diluents, need not appear on the 503A Bulks List to be eligible for use in compounding drug products and will not be included on the list.

B. Regulatory History of the 503A Bulks List

Section 503A of the FD&C Act was enacted in 1997. In the **Federal Register** of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the 503A Bulks List. In 1998, FDA received nominations for 41 different drug substances. Ten of these drug substances were the subject of an applicable USP or NF monograph or were components of FDA-approved drugs and did not need to go on the list to be used in compounding. After evaluating the nominated drug substances and consulting with the PCAC as required by section 503A(c)(2), FDA published a proposed rule listing 20 drug substances for potential inclusion on the initial section 503A Bulks List (64 FR 996, January 7, 1999) (the 1999 Proposed 503A Bulks List). The proposed rule also described 10 nominated drug substances that were still under consideration for the 503A Bulks List. The PCAC reconvened in May 1999 to discuss bulk drug substances included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791, April 22, 1999).

In February 2001, the U.S. Court of Appeals for the Ninth Circuit held that certain provisions of section 503A of the FD&C Act were unconstitutional restrictions on commercial speech. (See *Western States Med. Ctr.* v. *Shalala,* 238 F.3d 1090 (9th Cir. 2001).) Furthermore, the Ninth Circuit held that the advertising and solicitation provisions could not be severed from the rest of section 503A and, as a result, found section 503A of the FD&C Act to be invalid in its entirety. In April 2002, the U.S. Supreme Court affirmed the Ninth Circuit's decision that the advertising and solicitation provisions were unconstitutional; it did not, however, rule on the severability of section 503A of the FD&C Act. (See *Thompson* v. *Western States Med. Ctr.,* 535 U.S. 357 (2002).) In 2008, the U.S. Court of Appeals for the Fifth Circuit held that compounded drugs are subject to regulation by FDA, and that the advertising and solicitation provisions are severable from the rest of section 503A of the FD&C Act. (See *Medical Ctr. Pharm.* v. *Mukasey,* 536 F.3d 383 (5th Cir. 2008).)

Following a fungal meningitis outbreak in September 2012, FDA sought legislation to, among other things, resolve the split in the Circuits to clarify that section 503A of the FD&C Act was valid nationwide. On November 27, 2013, President Obama signed the Drug Quality and Security Act (Pub. L. 113–54) (DQSA), which contains important provisions relating to the oversight of human drug product compounding. Among other things, the DQSA removed from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the DQSA clarified that section 503A of the FD&C Act applies nationwide.

C. Requests for Nominations

Because of the amount of time that had passed between the publication of the 1999 proposed rule and the enactment of the DQSA, FDA felt it was necessary to begin again to develop the 503A Bulks List. In the **Federal Register** of December 4, 2013 (78 FR 72841), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on the 503A Bulks List.

Over 2,000 substances were nominated. However, many of those nominations were for a substance that is the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, were not for substances used in compounding as active ingredients, or did not include sufficient information for FDA to evaluate whether the substances should be proposed for inclusion on the 503A Bulks List. To improve the efficiency of the process for developing the 503A Bulks List, FDA reopened the nomination process in July 2014 (79 FR 37747, July 2, 2014) and provided a more detailed description about what information should be included in a nomination to support the Agency's evaluation. FDA stated that bulk drug substances that were previously nominated would not be further considered unless they were renominated and the new nominations were adequately supported. Substances that were already eligible for use in compounding or that were not adequately supported would not be placed on the list.

In response to that solicitation, approximately 740 unique substances were nominated. Of those substances, approximately 315 are components of an FDA-approved drug product or the

condition regarding bulk drug substances in section 503A(b)(1)(A)(i)(I) of the Act. Such a substance may only be used as a bulk drug substance under section 503A of the FD&C Act if it is a component of an FDA-approved drug product or is on the 503A Bulks List.

subject of an applicable USP or NF monograph. Such substances can be used in compounding under section 503A(b)(1)(A)(i)(I) and (II) of the FD&C Act and, therefore, are not eligible for inclusion on the 503A Bulks List.

At least one of the nominated substances is a finished drug product that was nominated by its brand name. Finished drug products are not eligible for the 503A Bulks List because they do not meet the definition of a bulk drug substance in § 207.3(4).

At least one of the nominated substances is a biological product subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) when used for the indication proposed in the nomination. This substance is not eligible for the 503A Bulks List because biological products subject to approval in a BLA under section 351 of the PHS Act are not eligible for the exemptions in section 503A of the FD&C Act. No biological products subject to approval in a BLA will be considered for the 503A Bulks List.

At least four of the nominated substances appear on the list published by FDA of substances that have been withdrawn or removed from the market because the drug products or components of the drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act) (Withdrawn or Removed List). Such substances cannot be used in compounding under section 503A of the FD&C Act, and therefore, are not eligible for inclusion on the 503A Bulks List.

One of the nominated substances has no currently accepted medical use and is included on Schedule I of the Controlled Substances Act (CSA) (21 U.S.C. 812(c)). The CSA does not allow possession or distribution of Schedule I substances (see 21 U.S.C. 841(a)(1) and 829), except for research purposes (see 21 U.S.C. 823(f)), and Schedule I substances will not be considered for the 503A Bulks List. Those desiring to do research on a Schedule I substance may apply to do so under an investigational new drug (IND) application.

Of the substances that are not components of an approved drug product or the subject of an applicable USP or NF monograph, finished drug products, biological products subject to licensure in a BLA, and do not appear on the Withdrawn or Removed List or Schedule I of the CSA, about 350 substances were nominated with insufficient supporting evidence for FDA to evaluate them.

The remaining substances may be eligible for inclusion on the 503A Bulks List and were nominated with sufficient supporting information for FDA to evaluate them. Ten of those substances have been evaluated and are discussed in section V. The rest will be discussed in future notices of proposed rulemaking (NPRMs) after they have been evaluated. Once the Agency completes its review of the substances that were nominated for the 503A Bulks List with adequate supporting information under the July 2, 2014, request for nominations, FDA will consider additional substances nominated for inclusion on the list if they are eligible and adequate supporting information is submitted to permit FDA to meaningfully evaluate them (see section III).

With regard to the substances nominated with sufficient supporting information for FDA to evaluate them, including the 10 nominated substances discussed in this proposed rule, FDA generally does not intend to take regulatory action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product, provided that the other conditions in section 503A and the FD&C Act are met, until the substance is addressed in a final rule. FDA is not applying this interim policy to a nominated substance however, if the Agency has identified the substance as posing a significant safety risk,[2] or if the substance was nominated without adequate support. For further information on this subject, see the guidance for industry entitled ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act'' (Ref. 1). As described in the guidance, the following categories of bulk drug substances are identified on FDA's Web site at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf:* (1) The substances nominated with sufficient supporting information that are under evaluation, (2) the substances nominated with sufficient supporting information but with which FDA has identified significant safety risks relating to the use of these bulk drug substances in compounding, and (3) the substances nominated with insufficient supporting evidence for FDA to evaluate them.

[2] This is not a determination regarding whether the substances will be added to the 503A Bulks list. FDA intends to make that determination after notice and comment rulemaking, as set forth in this proposal.

IV. Legal Authority

As described in the Background section, section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505 (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). One of the conditions that must be satisfied for a compounded drug to qualify for the exemptions under section 503A of the FD&C Act is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) Comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on the 503A Bulks List. See section 503A(b)(1)(A)(i) of the FD&C Act. Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(A)(i)(III) pertaining to the 503A bulks list, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. Section 503A(c)(2) of the FD&C Act requires the Secretary to issue the regulations in consultation with the USP, and to include in the regulation the criteria for such substances that shall include historical use, reports in peer reviewed journals, and any other criteria the Secretary identifies. Thus, section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our principal legal authority for this proposed rule.

V. Description of the Proposed Rule

FDA is proposing to add § 216.23 to title 21 of the Code of Federal Regulations (CFR) to set forth criteria to evaluate bulk drug substances for inclusion on the 503A Bulks List. Additionally, after considering 10 bulk drug substances for the 503A Bulks List,

FDA proposes to codify the initial 503A Bulks List to include 6 of the bulk drug substances that were considered and to identify 4 substances that were considered and would not be placed on the list. The criteria and the bulk drug substances considered for inclusion on the list are described in the paragraphs that follow.

A. Criteria for Evaluating Bulk Drug Substances for the 503A Bulks List

Section 503A(c)(2) of the FD&C Act provides that the criteria for determining which substances should appear on the 503A Bulks List shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary of Health and Human Services may identify. Consistent with the July 2, 2014, **Federal Register** notice (79 FR 37747) soliciting nominations for this list, and as presented to and discussed with the PCAC in February 2015 (Ref. 2), FDA proposes that the following criteria be used to evaluate the nominated substances:

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounded drug products;
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

In evaluating candidates for the 503A Bulks List under these criteria, the Agency proposes to use a balancing test. Specifically, the Agency proposes to consider each criterion in the context of the others and balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the 503A Bulks List.

Under the first criterion, the physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this criterion weigh against its inclusion on the 503A Bulks List because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency.

Under the second criterion, FDA would consider the safety issues raised by the use of each substance in pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. Thus, in evaluating list candidates, the Agency is likely to have at its disposal very limited information, or in some cases no information, of the type and quality that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances then, the Agency proposes to rely on available information, including reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity. The Agency would also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the safety criterion, FDA also proposes to consider the availability of approved drug products or drug products that follow an OTC monograph (OTC monograph products). The existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list when the toxicity of a particular substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

Under the third criterion, FDA proposes to consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, including reports in peer-reviewed medical literature, if any such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the candidates for the 503A Bulks List will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the Agency would take into account whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of one or more trials suggesting possible effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was not effective for a particular use (negative effectiveness data). When evaluating a bulk drug substance that is proposed for the treatment of a less serious illness, FDA would generally be more concerned about the safety of the substance than about its effectiveness. Thus, the availability of minimal effectiveness data, or the existence of mere anecdotal reports, would be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance that is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are approved drug products or OTC monograph products. In those cases, the existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list, and the availability of minimal effectiveness data, or the presence of negative effectiveness data, would weigh more heavily against placement on the list in FDA's balancing of the relevant criteria.

Under the fourth criterion, the historical use of the substance in pharmacy compounding, FDA proposes to consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, how widespread its use has been, including use in other countries, and any references in peer-reviewed medical literature. The Agency proposes that the longer a substance has been used in pharmacy compounding and the broader its use, the more this criterion will weigh in favor of inclusion of the substance on the list.

B. Methodology for Developing the 503A Bulks List

FDA reviewed the substances addressed in this proposed rule in the context of adequately supported nominated uses. In certain circumstances, FDA also reviewed substances in the context of unnominated or inadequately supported uses because, for example, such uses appear to be widespread, are intended to treat serious conditions, or pose serious risks to patients. The

information that FDA assessed to evaluate the substances addressed in this proposed rule under each of the proposed evaluation criteria was obtained from publicly available sources, including peer-reviewed medical literature. Some of this information was referenced in the nominations, and the remainder FDA gathered through independent searches of medical and pharmaceutical databases. FDA did not review raw data. The nature, quantity, and quality of the information FDA assessed varied considerably from substance to substance. In some cases, there were very little data. For other substances, reports in the literature were more plentiful and sometimes comprised hundreds or thousands of articles. In those cases, generally the Agency limited its review to a sample of the best literature sources available (*e.g.,* review articles in widely known, peer-reviewed journals; meta-analyses; reports of randomized controlled trials).

FDA's evaluation of the nominated substances was, necessarily, far less rigorous and less comprehensive than the Agency's review of drugs as part of the new drug approval process. The new drug approval process is conducted based on extensive data compiled and submitted with new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarketing evaluation of a specific drug formulation, the sponsor's chemistry and manufacturing controls, and the establishments where approved drugs will be manufactured. In contrast, these bulk drug substances will be evaluated only for possible use in compounded drugs.

Therefore, the proposed inclusion of a drug substance on the 503A Bulks List should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using the substances on the proposed list has been proven to be safe and effective under the standards required for Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally, or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

On February 23 and 24, 2015, and on June 17, 2015, FDA consulted with the PCAC created under section 503A(c)(1) of the FD&C Act, about the criteria proposed to evaluate substances nominated for the list and about the 10 substances that are addressed in this proposed rule (Refs. 2–4). The Agency has considered all of the PCAC's recommendations in developing this proposed rule, and the Agency intends to continue to consult with the PCAC in evaluating future candidates for the 503A Bulks List. The first 10 substances evaluated are addressed in this proposed rule. Going forward, FDA intends to publish NPRMs proposing additional substances be placed on the list or not placed on the list on a rolling basis as evaluations are completed. Depending on the length of time it takes to complete a rulemaking, multiple rulemakings may be ongoing simultaneously.

Section 503A of the FD&C Act requires that FDA create the 503A Bulks List by regulation, in consultation with the USP. See section 503A(c)(2) of the FD&C Act. To this end, FDA has been periodically meeting with USP and discussing the 503A Bulks List (Refs. 5 and 6). After publication of this NPRM, the public will have an opportunity to comment on the proposed rule. After considering the comments on this proposed rule submitted to the docket, FDA will issue the 503A Bulks List as a final rule, which will be codified in the CFR. The final version of the rule may include all, none, or only some of the substances proposed here for inclusion on the 503A Bulks List, depending on the comments received, and will also identify those substances the Agency has determined should not be placed on the list. The Agency may amend the 503A Bulks List to add or delete substances after further notice and comment rulemaking.

Individuals and organizations may petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published (see 21 CFR 10.30). Individuals and organizations may also nominate new substances for the 503A Bulks List or comment on nominated substances that have not yet been addressed in an NPRM via Docket No. FDA–2015–N–3534 while that docket is open.

C. Substances Proposed for Inclusion on the 503A Bulks List

Under section 503A(c)(2) of the FD&C Act, FDA is proposing that the following six bulk drug substances, which are neither the subject of a current applicable USP or NF monograph nor components of FDA-approved drugs, be included on the 503A Bulks List, and the drug products compounded with those substances may qualify for the exemptions provided for in section 503A of the FD&C Act (*i.e.,* from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act). When a salt or ester of an active moiety is listed, only that particular salt or ester may be used. The base compound and other salts or esters of the same active moiety must be evaluated separately for eligibility for the 503A Bulks List. Additionally, when a bulk drug substance is included on the 503A Bulks List subject to certain restrictions (for example, for a particular route of administration (*e.g.,* topical)), only dosage forms for that route of administration may be compounded with that bulk drug substance.

The following bulk drug substances are being proposed for the 503A Bulks List, to appear in § 216.23(a) of Title 21 of the CFR:

1. Brilliant Blue G

Brilliant Blue G, also known as Coomassie Brilliant Blue G-250,[3] was evaluated for use as a dye used in staining for visualization during ophthalmic procedures. It is well characterized physically and chemically. There are potential mutagenic and carcinogenic concerns associated with Brilliant Blue G; however, those concerns are mitigated in clinical use because the dye is immediately washed out of the eye after administration, and tissue that is stained with the dye is removed as part of the surgical procedure. Published clinical trials provide some evidence for efficacy of Brilliant Blue G in staining the internal limiting membrane. Brilliant Blue has had relatively widespread use for staining the internal limiting membrane during retinal surgery for approximately 10 years. There is one product that is FDA-approved for staining the internal limiting membrane and the anterior capsule.

FDA proposed to the PCAC that Brilliant Blue G be included on the 503A Bulks List (Ref. 7), and at its meeting on June 17, 2015, the PCAC voted to include Brilliant Blue G on the list (Ref. 4). The proposed rule would place Brilliant Blue G on the 503A Bulks List.

2. Cantharidin

Cantharidin, which is obtained from various species of blister beetle, was

[3] While there are other substances referred to by the name ''Brilliant Blue,'' only Coomassie Brilliant Blue G-250 (CAS RN 6104-58-1, UNII M1ZRX790SI) was evaluated, and the Agency is proposing only that substance for inclusion on the 503A Bulks List. The other substances referred to as ''Brilliant Blue'' would have to be nominated and separately evaluated for consideration for inclusion on the 503A Bulks List.

evaluated for topical use [4] in the treatment of warts and molluscum contagiosum. It is well characterized physically and chemically. Cantharidin is extremely toxic, due to its potential for severe irritation. However, clinical data accumulated since 1958 indicate that, with careful use under physician direction, toxicities observed with cantharidin, are no worse than and sometimes less severe than those seen with other destructive modalities in the treatment of molluscum contagiosum and warts. Evidence of some efficacy of cantharidin in the treatment of warts and molluscum contagiosum has been reported in the literature. It appears to have been widely used to treat molluscum contagiosum and warts since the 1950s. There are no approved prescription or OTC monograph products for molluscum contagiosum. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products containing salicylic acid are available.

FDA proposed to the PCAC that cantharidin be included on the 503A Bulks List for topical use only (Ref. 8). At the PCAC meeting on February 24, 2015, the PCAC voted to include cantharidin on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place cantharadin on the 503A Bulks List for topical use only.

3. Diphenylcyclopropenone (DPCP)

DPCP was evaluated for topical use in the treatment of alopecia areata and nongenital warts. It is well characterized physically and chemically but degrades readily by hydrolysis in an alcoholic base or exposure to light. Known safety concerns about the use of DPCP are limited to reported adverse effects primarily due to its action as a contact sensitizer to elicit contact dermatitis. Evidence of some efficacy of DPCP in the treatment of alopecia areata and recalcitrant nongenital warts has been reported in the literature. DPCP has been used to treat resistant non-genital warts and alopecia areata for over 30 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no approved prescription drug products outside of the genital area. A variety of OTC monograph products are available containing salicylic acid at percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that DPCP be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include DPCP on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place DPCP on the 503A Bulks List for topical use only.

4. N-acetyl-D-glucosamine (NAG)

NAG, also known as acetyl-D glucosamine or N-acetyl glucosamine, was evaluated for topical use in the treatment of hyperpigmentation and other skin conditions. It is well characterized physically and chemically. Topical use of NAG has been associated with relatively minor and infrequent side effects. Studies have indicated that NAG may be effective for reducing diffuse and local facial hyperpigmentation. NAG has been used topically for the treatment of hyperpigmentation since the mid-2000s. There are FDA-approved drug products indicated for the treatment of hyperpigmentation and other skin conditions, which are not serious or life-threatening conditions.

FDA proposed to the PCAC that NAG be included on the 503A Bulks List for topical use only (Ref. 7). At the PCAC meeting on June 17, 2015, the PCAC voted to include NAG on the list (Ref. 4). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place NAG on the 503A Bulks List for topical use only.

5. Squaric Acid Dibutyl Ester (SADBE)

SADBE was evaluated for topical use in the treatment of alopecia areata and recalcitrant nongenital warts. It is well characterized physically and chemically but hydrolyzes readily in the presence of water. The adverse effects from use of SADBE are primarily related to its action as contact sensitizer. Evidence of some efficacy of SADBE in the treatment of recalcitrant nongenital warts and alopecia areata has been reported in the literature. SADBE has been used in the treatment of resistant nongenital warts and alopecia areata for 30 to 40 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products are available containing salicylic acid at percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that SADBE be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include SADBE on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place SADBE on the 503A Bulks List for topical use only.

6. Thymol Iodide

Thymol iodide was evaluated for use as a topical treatment for ulcerations and skin infections, as well as an intrapleural treatment for pleural effusions. It is well characterized physically and chemically. Reports indicate that it has been used without major complications. Literature reports some efficacy of thymol iodide for pleural effusions, which are serious and can be life-threatening conditions. Data regarding the effectiveness of thymol iodide in compounding for topical use on wounds or ulcers in various skin conditions is limited; however, these skin conditions generally are not serious or life-threatening. Thymol iodide has been in use for over 100 years. Regarding use as an antiseptic in surgery and use as an external application to wounds or ulcers in various skin conditions, approved and OTC monograph products are available. There are also FDA-approved products available to treat malignant pleural effusions.

FDA proposed to the PCAC that thymol iodide be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted to include thymol iodide on the list (Ref. 2). Because the supported nominations were limited to the topical use of this substance, and because pleural effusions are serious and potentially life-threatening conditions for which there are approved products available, the proposed rule would place thymol iodide on the 503A Bulks List for topical use only.

D. Substances Considered and Not Proposed for Inclusion on the 503A Bulks List

FDA is proposing that four of the bulk drug substances that it has evaluated not be included on the 503A Bulks List. Bulk drug substances that are considered for the 503A Bulks list but not placed on the list cannot be used to compound drug products that would qualify for the exemptions in section 503A. If a prescribing practitioner nevertheless believes that a patient should be treated with a drug product compounded from such a bulk drug substance, it may be possible to obtain

[4] Except where specified otherwise, ''topical use'' means for application on the skin only and does not include oral, intravaginal, or ophthalmic use.

the drug under an IND. For information about the requirements for proceeding under an IND, visit FDA's Web site at *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm.*

The four bulk drug substances that have been evaluated and that FDA is not proposing to place on the list, and the reasons for that proposal, are as follows:

1. Oxitriptan

Oxitriptan, also known as 5-hydroxytryptophan (5-HTP), was evaluated as a treatment for depression and insomnia. It is a hydroxylated form of a naturally occurring amino acid, tryptophan. Oxitriptan is well characterized physically and chemically. However, there are significant safety concerns related to its use. Based upon its mechanism of action, concomitant use of oxitriptan with antidepressant drugs could result in serotonin syndrome, a serious and life-threatening drug interaction. Additionally, medications used to treat depression have been linked to an increase in suicidal thinking and behavior. There are no data to suggest that oxitriptan would be free of similar risks, and compounded drugs do not include labeling that would adequately warn physicians and patients of such risks. Other potential adverse reactions include moderate gastrointestinal effects, which are common upon administration of oxitriptan.

Data supporting the efficacy of oxitriptan for depression are limited, and there is no evidence to support long-term efficacy of oxitriptan for the treatment of this chronic disease. Depression is a serious and potentially life-threatening condition, and there are multiple FDA-approved antidepressants that have been shown to be safe and effective in their approved forms that are appropriately labeled. Regarding the use of oxitriptan to treat insomnia, the clinical trials examining insomnia were too poorly designed and/or executed to assess efficacy. There are multiple FDA-approved drug products available for the treatment of insomnia. The length of time oxitriptan has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physiochemical characteristics, the safety concerns, lack of evidence of effectiveness, and historical use of oxitriptan weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal regarding this substance is based on the seriousness of the safety concerns related to the use of oxitriptan for depression in lieu of, or causing a delay in the use of an approved product, the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking an oxitriptan product, and the availability of approved drug products for the treatment of depression, a potentially life-threatening condition. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). At its meeting on June 17, 2015, the PCAC voted not to include oxitriptan on the list (Ref. 4). The proposed rule would not place oxitriptan on the 503A Bulks List.

2. Piracetam

Piracetam was evaluated as a treatment for enhancing cognitive skills in treating a variety of cognitive disorders, including Alzheimer's disease. It has also been studied for treatment of coagulation disorders and vertigo. It is well characterized physically and chemically. Piracetam is approved in the United Kingdom (UK) as a prescription drug for the adjunctive treatment of cortical myoclonus. The labeling of the UK product identifies that the drug is renally excreted, that the dosage should be adjusted in the presence of renal disease, and that it is contraindicated in end-stage renal disease. Piracetam acts by multiple mechanisms to prolong bleeding time and is therefore not recommended for use by individuals with medical conditions that prolong bleeding time or that are taking concomitant anticoagulants or other medications that prolong bleeding (Ref. 9). Piracetam is not recommended for women who are pregnant, planning to become pregnant, or breastfeeding, because, according to the UK product's labeling, the drug has been shown to cross the placenta and be excreted in human milk. It is also recommended that individuals required to restrict their salt intake avoid piracetam (id.).

Piracetam was assessed for the treatment of mild cognitive impairment, a potential component of Alzheimer's disease, in a large, well-conducted, controlled clinical trial that failed to demonstrate efficacy. Studies of the efficacy of piracetam for other indications have been inconclusive, many of which were poorly designed or executed, or used flawed statistical methods to analyze the results. Piracetam's regulatory approval in the UK for the treatment of cortical myoclonus, which is not among the uses for which piracetam was nominated, was based on a single center, retrospective review of 40 patients treated with piracetam (id.). FDA-approved products are available for treatment of the conditions, and conditions related to, those for which piracetam was nominated, for example, for Alzheimer's disease, which is frequently preceded by mild cognitive impairment. Regarding historical use, piracetam has been available for approximately 40 years.

On balance, the physiochemical characteristics, safety concerns, inconclusive evidence of effectiveness, and historical use of piracetam weigh against inclusion of this substance on the list. In particular, the Agency's proposal regarding this substance is based on the limited evidence of benefit associated with piracetam, the seriousness of the conditions for which piracetam was nominated to be used, and the availability of safe and effective FDA-approved medications for many of these uses. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted not to include piracetam on the list (Ref. 3). The proposed rule would not place piracetam on the 503A Bulks List.

3. Silver Protein Mild

Silver protein mild, also known as mild silver protein, was evaluated for use as an anti-infective agent for ophthalmic use. Silver protein mild is not well characterized because the term ''silver protein mild'' is used to refer to a variety of different drug products. There are also safety concerns associated with the use of silver protein mild. It can cause argyria, which is a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs. Regarding effectiveness, silver protein mild has been found to be inferior to another treatment in clinical trials. A number of FDA-approved anti-infective agents for ophthalmic use are available and have been shown to be both safe and effective. While it has a long history of use, dating back to the early 1900s, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives.

On balance, the physiochemical characteristics, safety issues, questionable effectiveness, and historical use of silver protein mild weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal is based on the facts that silver protein mild is not well characterized, that in clinical trials it has been found to be inferior to another treatment and

numerically inferior to no treatment at all, and that chronic use may result in permanent discoloration of the conjunctiva, cornea, and/or lens. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted not to include silver protein mild on the list (Ref. 2). The proposed rule would not place silver protein mild on the 503A Bulks List.

4. Tranilast

Tranilast, an antiallergenic agent, was evaluated for the treatment of allergic disorders, arthritis, dry eye syndrome, keloids, and hypertrophic scars. It is approved in South Korea and Japan for the treatment of asthma, keloids, and hypertrophic scarring, and as an ophthalmic solution for allergic conjunctivitis. It is well characterized physically and chemically. However, there are significant safety concerns associated with its systemic administration. In a well-controlled clinical trial with nearly 12,000 participants (the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial) (Ref. 10), tranilast was associated with significantly elevated liver enzymes (three times the upper limit of normal) in 11 percent of patients within 1 to 3 months of drug initiation, as well as anemia, renal failure, rash, and dysuria.[5] Liver toxicity is of particular concern because many of the conditions for which tranilast was nominated are chronic conditions. While there is some evidence that tranilast may be effective for allergic disorders, evidence of effectiveness for other uses is either not available or inconclusive. For allergy, arthritis, and ophthalmic indications, there are numerous FDA-approved and OTC monograph products. The length of time tranilast has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physiochemical characteristics, safety concerns, lack of evidence of effectiveness, and historical use of tranilast weigh against inclusion of this substance on the 503A Bulks List, particularly given the seriousness of the safety concerns related to hepatotoxicity of tranilast and contraindications in pregnant and breastfeeding women, the availability of approved products for most of the proposed uses, and the lack of evidence that tranilast is effective. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). However, at its meeting on June 17, 2015, the PCAC voted to include tranilast on the list for topical use only (Ref. 4).

Subsequent to that meeting, FDA reviewed the topical use of tranilast further. It obtained the label of the Japanese tranilast product, RIZABEN, but found no information on the transdermal absorption or other pharmacokinetics of tranilast when applied topically to healthy or diseased human skin (Ref. 11). The labeling of the Japanese product identifies a number of safety concerns, including a contraindication in pregnant women, especially during the first trimester of pregnancy, and in those who might be pregnant, due to evidence of teratogenicity in animal studies (id.). The labeling also states that tranilast is detected in breast milk and should be avoided by breastfeeding women. In addition, the RIZABEN label lists a drug interaction with warfarin and identifies a number of serious adverse events, particularly those that are hematologic in nature (leukopenia, thrombocytopenia, anemia, hemolytic anemia), associated with the oral use of tranilast. Safety information regarding other routes of administration is limited.

FDA also noted evidence that some increases in some liver function tests (bilirubin) are explained by tranilast inhibition of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) especially in patients with a genotype for Gilbert's Disease. Increases in liver transaminases observed with tranilast are not typically seen with inhibition of UGT1A1. It is speculated that tranilast impairs the metabolism of drugs that are metabolized by UGT1A1. If these drugs are associated with transaminase elevations, inhibiting the drug's metabolism may lead to liver transaminitis.

As was found in the Agency's initial review and presented to the PCAC, there is no persuasive information available regarding the safety or effectiveness of topical tranilast. FDA has identified only two reports in the literature describing the efficacy and safety of tranilast administered topically for the treatment of keloids and hypertrophic scars (Refs. 12 and 13). One of those studies was an open-label trial, and the other was a case series. Between the two studies, only five patients were exposed to topical tranilast.

As stated previously, FDA has serious concerns about the safety of tranilast when administered orally. The Agency has insufficient information about the systemic absorption of topical tranilast formulations to determine whether topical administration of the drug product would present the same safety concerns. Given the lack of information available about the safety and efficacy of topical tranilast, and safety concerns related to the oral use of this product, the proposed rule would not place tranilast on the 503A Bulks List.

VI. Proposed Effective Date

The Agency proposes that any final rule based on this proposal will become effective 30 days after the date of publication of the final rule in the **Federal Register**.

VII. Analysis of Environmental Impact

FDA has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to

[5] During the PCAC meeting on June 17, 2015, the PRESTO trial was criticized by one of the tranilast nominators as having insufficiently accounted for the medical history of the subjects, among other things (see Ref. 4). To the contrary, the five-arm trial design appears to have been properly controlled for the patients' various medical conditions, and signals of liver toxicity were consistent across arms (see Ref. 10).

prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

TABLE 1—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT

Category	Primary estimate	Low estimate	High estimate	Units year dollars	Discount rate (%)	Period covered (years)	Notes
Benefits							
Annualized Monetized $ mil/year.	Not Estimated (N.E.).				7	10	
Annualized Monetized $ mil/year.	N.E				3	10	
Annualized Quantified.	N.E				7		
Annualized Quantified.	N.E				3		
Qualitative	Not including four bulk drug substances from the 503A Bulks List would limit the use of potentially ineffective or unsafe unapproved drugs.						
Costs							
Annualized Monetized $ mil/year.	N.E				7	10	
Annualized Monetized $ mil/year.	N.E				3	10	
Annualized Quantified.	$118 to $235 one-time per firm costs.			2014	7		
Annualized Quantified.	$118 to $235 one-time per firm costs.			2014	3		
Qualitative							
Transfers							
Federal Annualized Monetized $ mil/year.					7		
Federal Annualized Monetized $ mil/year.					3		
From/To	From:			To:			
Other Annualized $ mil/year.	N.E				7		
Other Annualized Monetized $ mil/year.	N.E				3		

TABLE 1—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT—Continued

Category	Primary estimate	Low estimate	High estimate	Units year dollars	Discount rate (%)	Period covered (years)	Notes
From/To	From: Producers of bulk drug substances not proposed for inclusion and compounding pharmacies using these substances.	.....	.....	To: Producers of alternative treatments, consumers, using these treatments and payers for these treatments.	.....	.....	.....
Effects							
State, Local, and/or Tribal Government: No effect. Small Business: Unknown effect. Wages: No effect. Growth: No effect.							

The Economic Analysis of Impacts of the proposed rule performed in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act is available at *http://www.regulations.gov* under the docket number for this proposed rule (Ref. 14) and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.* We invite comments on this analysis.

A. Summary of the Costs of the Rule

We lack data on the scope of the current use of the affected bulk drug substances and the number of firms that would be affected by the rule. Without this information, we cannot quantify the total potential costs of the proposed rule. Potential costs include administrative costs, additional costs for consumers and payers if alternative therapies are more costly than the affected compounded drug products, and a potential loss of producer surplus if producers use additional resources in response to the rule. We estimate that each affected firm would spend 1 to 2 hours on administrative costs to read and understand the rule. The average hourly wage for a pharmacist in 2014 equals about $57, or $114 including 100 percent overhead. Thus, each affected firm would incur administrative costs that range from $118 to $235. We request comment on the potential costs and number of firms affected by the proposed rule.

B. Summary of the Benefits of the Rule

The benefits of the rule are unquantified. We include a qualitative discussion of potential benefits. For consumers who switch to more effective treatments, there would be benefits as consumers experience better health outcomes than they do currently.

C. Summary of the Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless the Agency can certify that the proposed rule would have no significant impact on a substantial number of small entities. The Small Business Administration (SBA) establishes thresholds for small entities by North American Industry Classification System (NAICS); the SBA considers small any entity below these thresholds. Firms affected by the proposed rule would fall into three major industries, NAICS 325412 Pharmaceutical Preparation Manufacturing, NAICS 424210 Drugs and Druggists' Sundries Merchant Wholesalers, and NAICS 446110 Pharmacies and Drug Stores. The thresholds for these industries are 750 employees for NAICS 325412, 100 employees for NAICS 424210, and annual sales of $27.5 million for NAICS 446110.

We lack data on the number or size of manufacturers, wholesalers, and compounding pharmacies that would be affected by the proposed rule. Moreover, we find little evidence of widespread use of four bulk drug substances not proposed for inclusion on the 503A Bulks List. This suggests that the impact of the rule would likely not be significant on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we believe that the proposed rule would not have a significant economic impact on a substantial number of small entities, but the impacts are uncertain. We request detailed comments and data on the number of small entities that would be affected by the proposed rule, as well as data on the economic impact of the proposed rule on these small entities.

IX. Paperwork Reduction Act of 1995

The submission of comments on this proposed rule would be submissions in response to a **Federal Register** notice, in the form of comments, which are excluded from the definition of ''information'' under 5 CFR 1320.3(h)(4) of Office of Management and Budget regulations on the Paperwork Reduction Act (*i.e.,* facts or opinions submitted in response to general solicitations of comments from the public, published in the **Federal Register** or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency's full consideration of the

comment). The proposed rule contains no other collection of information.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov.* FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. FDA, ''Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act,'' (*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf*), 2016.

2. FDA, Transcript of the February 23, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015, (*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf*).

3. FDA, Transcript of the February 24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf*).

4. Transcript of the June 17, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015, (*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf*).

5. Memorandum to File on FDA Consultations with USP, September 26, 2016.

6. Letter from USP to FDA, October 7, 2016.

7. FDA Briefing Document for the June 17–18, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf*).

8. FDA Briefing Document for the February 23–24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf*).

9. Obeso, J. A., et al., ''Piracetam in the Treatment of Different Types of Myoclonus,'' *Clinical Neuropharmacology,* 11(6): 529–536, 1988.

10. Holmes, D.R., Jr., M. Savage, J.M. LaBlanche, et al., ''Results of Prevention of RESt enosis with Tranilast and its Outcomes (PRESTO) Trial,'' *Circulation,* 106(10): 1243–1250, 2002.

11. FDA Supplemental Review of Topical Tranilast, April 25, 2016.

12. Shigeki, S., T. Murakami, N. Yata, and Y. Ikuta, ''Treatment of Keloid and Hypertrophic Scars by Iontophoretic Transdermal Delivery of Tranilast,'' *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery,* 31(2): 151–159, 1997.

13. Banov, D., F. Banov, and A.S. Bassani, ''Case Series: The Effectiveness of Fatty Acids From Pracaxi Oil in a Topical Silicone Base for Scar and Wound Therapy,'' *Dermatology and Therapy,* 4(2): 259–269, 2014.

14. Economic Analysis of Impacts.

List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, the Food and Drug Administration proposes to amend 21 CFR part 216 as follows:

PART 216—HUMAN DRUG COMPOUNDING

■ 1. The authority citation for part 216 is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.

■ 2. The heading for part 216 is revised to read as set forth above.

■ 3. Section 216.23 is added to read as follows:

§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

(a) The following bulk drug substances can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

Brilliant Blue G, also known as Coomassie Brilliant Blue G–250.

Cantharidin (for topical use only).

Diphenylcyclopropenone (for topical use only).

N-acetyl-D-glucosamine (for topical use only).

Squaric acid dibutyl ester (for topical use only).

Thymol iodide (for topical use only).

(b) After balancing the criteria set forth in paragraph (c) of this section, FDA has determined that the following bulk drug substances will not be included on the list of substances that can be used in compounding set forth in paragraph (a) of this section:

Oxitriptan.

Piracetam.

Silver Protein Mild.

Tranilast.

(c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:

(1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;

(3) The available evidence of the effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and

(4) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Dated: December 9, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–30109 Filed 12–15–16; 8:45 am]

BILLING CODE 4164–01–P

APPENDIX 3: Final Rule: List Of Bulk Drug Substances That Can Be Used To Compound Drug Products In Accordance With Section 503A Of The Federal Food, Drug, and Cosmetic Act (February 2019)

(d) Subject

Joint Aircraft System Component (JASC) Code 7230, Turbine Engine Compressor Section.

(e) Unsafe Condition

This AD was prompted by the FAA's determination that inspections need to be expanded to all EA GP7270 and GP7277 turbofan engines. We are issuing this AD to detect defects, damage, and cracks that could result in an uncontained failure of the engine fan hub assembly. The unsafe condition, if not addressed, could result in uncontained failure of the engine fan hub assembly, damage to the engine, and damage to the airplane.

(f) Compliance

Comply with this AD within the compliance times specified, unless already done.

(g) Required Actions

Within 3,000 cycles since new after the effective date of this AD, or by August 15, 2019, whichever is later:

(1) For engine fan hubs at the low-pressure compressor (LPC) module assembly level:

(i) Perform a visual inspection of the engine fan hub assembly, in accordance with the Accomplishment Instructions, For Fan Hubs at LPC Module Assembly Level, paragraphs 1.A.(1), 1.A.(4), and 1.A.(6)(a), of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(ii) Perform an eddy current inspection (ECI) of the engine fan hub blade slot bottoms and front edges, in accordance with the Accomplishment Instructions, For Fan Hubs at LPC Module Assembly Level, paragraphs 2.A and 2.B, of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(2) For engine fan hub assemblies at the piece part level:

(i) Perform a visual inspection of the engine fan hub assembly, in accordance with the Accomplishment Instructions, For Fan Hubs at Piece Part Level, paragraphs 1.A.(1) and 1.A.(3), of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(ii) Perform an ECI of the engine fan hub blade slot bottoms and front edges, in accordance with the Accomplishment Instructions, For Fan Hubs at Piece Part Level, paragraphs 2.A and 2.B, of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(3) For engine fan hub assemblies installed in an engine (on-wing or off-wing):

(i) Perform a visual inspection of the engine fan hub assembly, in accordance with the Accomplishment Instructions, For Fan Hubs Installed in an Engine, paragraphs 1.C.(1), 1.C.(5), and 1.C.(7)(a), of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(ii) Perform an ECI of the engine fan hub blade slot bottoms and front edges, in accordance with the Accomplishment Instructions, For Fan Hubs Installed in an Engine, paragraphs 1.D.(1) and 1.D.(2), of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(4) If the engine fan hub assembly visual inspection reveals defects or damage to the engine fan hub assembly that are found outside the serviceable limits specified in Table 6 in the Accomplishment Instructions of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018, remove the engine fan hub assembly from service and replace with a part that is eligible for installation, before further flight.

(5) If the engine fan hub assembly ECI results in a rejectable indication, per the Appendix, Added Data, of EA ASB EAGP7–A72–389, Revision No. 3, dated October 18, 2018, remove the engine fan hub assembly from service and replace with a part that is eligible for installation, before further flight.

(h) Credit for Previous Actions

You may take credit for the inspection required by paragraph (g) of this AD if you performed the inspection before the effective date of this AD, using EA ASB EAGP7–A72–389, Original Issue, dated December 19, 2017; EA ASB EAGP7–A72–389, Revision No. 1, dated January 19, 2018; or EA ASB EAGP7–A72–389, Revision No. 2, dated April 17, 2018.

(i) Alternative Methods of Compliance (AMOCs)

(1) The Manager, ECO Branch, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or local Flight Standards District Office, as appropriate. If sending information directly to the manager of the certification office, send it to the attention of the person identified in paragraph (j) of this AD. You may email your request to: *ANE-AD-AMOC@faa.gov.*

(2) Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the local flight standards district office/certificate holding district office.

(3) AMOCs approved for AD 2018–11–16 (83 FR 27891, June 15, 2018) are approved as AMOCs for the corresponding provisions of this AD.

(j) Related Information

For more information about this AD, contact Matthew Smith, Aerospace Engineer, ECO Branch, FAA, 1200 District Avenue, Burlington, MA, 01803; phone: 781–238–7735; fax: 781–238–7199; email: *matthew.c.smith@faa.gov.*

(k) Material Incorporated by Reference

(1) The Director of the Federal Register approved the incorporation by reference (IBR) of the service information listed in this paragraph under 5 U.S.C. 552(a) and 1 CFR part 51.

(2) You must use this service information as applicable to do the actions required by this AD, unless the AD specifies otherwise.

(i) Engine Alliance (EA) Alert Service Bulletin EAGP7–A72–389, Revision No. 3, dated October 18, 2018.

(ii) [Reserved]

(3) For EA service information identified in this AD, contact Engine Alliance, 411 Silver Lane, East Hartford, CT, 06118; phone: 800–565–0140; email: *help24@pw.utc.com;* website: *www.engineallianceportal.com.*

(4) You may view this service information at FAA, Engine and Propeller Standards Branch, 1200 District Avenue, Burlington, MA, 01803. For information on the availability of this material at the FAA, call 781–238–7759.

(5) You may view this service information that is incorporated by reference at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to: *http://www.archives.gov/federal-register/cfr/ibr-locations.html.*

Issued in Burlington, Massachusetts, on February 12, 2019.

Robert J. Ganley,

Manager, Engine & Propeller Standards Branch, Aircraft Certification Service.

[FR Doc. 2019–02654 Filed 2–15–19; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA–2016–N–3464]

RIN 0910–AH29

List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a final rule to establish criteria for and identify an initial list of bulk drug substances that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. Specifically, the Agency is placing six bulk drug substances on the list. This final rule also identifies four bulk drug substances that FDA has considered and is not including on the list. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of a future rulemaking.

DATES: This rule is effective March 21, 2019.

ADDRESSES: For access to the docket to read background documents or

comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the heading of this final rule into the ''Search'' box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Rosilend Lawson, Center for Drug Evaluation and Research, Office of Unapproved Drugs and Labeling Compliance, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5197, Silver Spring, MD 20993, 240–402–6223, *Rosilend.Lawson@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Final Rule

FDA is amending title 21 of the Code of Federal Regulations to add a list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as ''the 503A Bulks List'' or ''the list''). Bulk drug substances that appear on the 503A Bulks List can be used to compound drug products subject to the conditions of section 503A, although those substances are not the subject of an applicable USP or NF monograph or components of approved drug products.

B. Summary of the Major Provisions of the Final Rule

In this final rule, FDA is establishing the criteria for evaluation of bulk drug substances for inclusion on the 503A Bulks List: (1) The physical and chemical characterization of the substance; (2) any safety issues raised by the use of the substance in compounded drug products; (3) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and (4) historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

Based on the results of its evaluation of nominated bulk drug substances to date, as well as consultation with the Pharmacy Compounding Advisory Committee (PCAC) and USP, FDA is including six bulk drug substances on the list: Brilliant Blue G, also known as Coomassie Brilliant Blue G–250; cantharidin (for topical use only); diphenylcyclopropenone (for topical use only); N-acetyl-D-glucosamine (NAG) (for topical use only); squaric acid dibutyl ester (for topical use only); and thymol iodide (for topical use only). FDA is also identifying four other bulk drug substances that will not be included on the list: Oxitriptan, piracetam, silver protein mild, and tranilast. Drugs compounded with these substances will not qualify for the 503A exemptions and cannot be used in compounding under section 503A of the FD&C Act.

C. Legal Authority

Section 503A, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serves as our principal legal authority for this final rule.

D. Costs and Benefits

FDA is establishing criteria for evaluating inclusion of bulk drug substances on the 503A Bulks List, placing six bulk drug substances on the 503A Bulks List, and not including four bulk drug substances on the 503A Bulks List. The present value of the costs of the final rule equals $3.33 million at a 7 percent discount rate and $3 million at a 3 percent discount rate. The final rule will result in annualized costs of $0.42 million at a 7 percent discount rate, or $0.31 million at a 3 percent discount rate. Because we lack sufficient information to quantify many of the costs and the benefits of this final rule, we also include a qualitative description of potential benefits and potential costs. We expect that the rule would affect compounding pharmacies and certain other entities that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected drug substances, and payers that cover these drug products or alternative drug products.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/ acronym	What it means
APA	Administrative Procedure Act.
5-HTP	5-hydroxytryptophan.
CFR	Code of Federal Regulations.
DQSA	Drug Quality and Security Act.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FDA	Food and Drug Administration.
GRAS	Generally recognized as safe.
HPUS	Homeopathic Pharmacopeia of the United States.
IND	Investigational new drug.
NAG	N-acetyl-D-glucosamine.
NDA	New drug application.
NF	National Formulary.
NPRM	Notice of proposed rulemaking.
OTC	Over-the-counter.
PCAC	Pharmacy Compounding Advisory Committee.
PDUFA	Prescription Drug User Fee Act.
USP	United States Pharmacopeia.

III. Background

A. Need for and History of This Rulemaking

Section 503A describes the conditions under which a compounded drug product qualifies for exemptions from certain sections of the FD&C Act. Those conditions include that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) Comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary of Health and Human Services (the Secretary); or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.) This final rule establishes criteria for evaluating bulk drug substances for inclusion on the 503A Bulks List and identifies six bulk drug substances the Secretary is placing on the list. The Agency considered four other bulk drug substances and is not including those substances on the 503A Bulks List. Additional bulk drug substances are under evaluation, and new substances may be added to the list through subsequent rulemaking.

The definitions that are relevant to this final rule are set forth in the notice of proposed rulemaking (NPRM) published in the **Federal Register** of

December 16, 2016 (81 FR 91071). The 2016 proposed rule also includes a complete history of this rulemaking. In that proposed rule, FDA discussed the 10 bulk drug substances nominated for inclusion on the 503A Bulks List that are the subject of this final rule, along with the criteria FDA proposed to use when determining whether to place bulk drug substances on the 503A Bulks List.

Under this final rule, drug products compounded with the six substances that are being placed on the 503A Bulks List qualify for the 503A exemptions if the conditions of section 503A of the FD&C Act are met. In contrast, drugs compounded with the other four substances evaluated in this rulemaking—which are not being placed on the 503A Bulks List— do not qualify for the 503A exemptions and cannot be used in compounding under section 503A of the FD&C Act. As discussed in the 2016 proposed rule and in the guidance for industry entitled ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act'' (Interim Policy Guidance) (Ref. 1), FDA generally has not intended to take regulatory action for the use of certain substances, including the 10 substances that are the subject of this final rule, while those substances were being considered for inclusion on the 503A Bulks List (interim policy). Since the rulemaking is now complete for these 10 nominated substances, the interim policy no longer applies to those substances.

B. Summary of Comments to the Proposed Rule

We received eight substantively relevant, unique comments to the 2016 proposed rule. The comments addressed FDA's proposals on the criteria for evaluating bulk drug substances for inclusion on the 503A Bulks List, including some comments on how FDA has been using the criteria in practice. The comments also addressed FDA's proposals on particular bulk drug substances. In addition to these topics, which addressed the language proposed to be included in the Code of Federal Regulations (CFR), commenters addressed a variety of topics related to FDA's evaluation of bulk drug substances, including procedural issues related to meetings of the PCAC, and compounding policies generally.

IV. Legal Authority

As described in the Background section, section 503A describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505 (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). One of the conditions that must be satisfied for a compounded drug to qualify for the exemptions under section 503A of the FD&C Act is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounding drug products using bulk drug substances, must use bulk drug substances that: (1) Comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appear on the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.) Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement certain parts of section 503A, and that before issuing regulations to implement section 503A(b)(1)(A)(i)(III) pertaining to the 503A Bulks List, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. Section 503A(c)(2) of the FD&C Act requires the Secretary to issue the regulations in consultation with the USP, and to include in the regulation the criteria for such substances that shall include historical use, reports in peer-reviewed journals, and any other criteria the Secretary identifies. Thus, section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our principal legal authority for this final rule.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received 12 total comments posted to the docket for the proposed rule by the close of the comment period. Of the 12 comments received, 3 addressed subjects other than the proposed rule, and 9 were related to the proposed rule. Of the nine comments substantively related to the proposed rule, one was a duplicate. Of the eight unique, substantively relevant comments received, each discussed one or more issues. We received comments from consumers; trade organizations, including those representing compounders and clinicians with particular specialties; a company that sells bulk drug substances and other materials for compounding; and other organizations.

We describe and respond to the issues raised in the comments in sections V.B. and V.C. of this document. We have consolidated and grouped the issues raised in the comments, and assigned each issue a ''comment number'' to help distinguish among different issues raised in the comments. We have grouped similar issues raised in the comments together under the same comment number, and, in some cases, we have separated different issues discussed in the same comment and designated them with distinct comment numbers for purposes of our responses. The comment number assigned to each issue or topic is purely for organizational purposes and does not signify the value or importance of the issue or the order in which comments were received.

We received some comments that raised issues that are outside the scope of this rulemaking (*e.g.,* animal testing, access to compounded drug products as ''office stock,'' FDA's interpretation of the phrase ''clinical need'' as used in section 503B of the FD&C Act, competition and drug pricing). To the extent issues raised in comments are unrelated to this rulemaking, we do not respond to those comments.

B. Description of General Comments and FDA Response

(Comment 1) Some comments made general remarks supporting the proposed rule. These comments supported the proposed criteria, the proposed placement of the six substances listed above on the 503A Bulks List, the proposal not to include the four substances listed above on the 503A Bulks List, and FDA's Interim Policy Guidance.

(Response 1) We appreciate the support expressed in the comments received.

C. Specific Comments and FDA Response

1. Proposed Criteria

(Comment 2) Some comments objected to the proposed criteria as too broad and vague to provide standards by which ingredients will be judged. For example, one comment stated that FDA fails to define what constitutes ''significant'' toxicity or ''other safety concerns,'' which are vague and give FDA too much discretion. The comments stated that the proposed

criteria will lead to highly subjective decisions.

(Response 2) We disagree and find no basis to change the criteria proposed in the 2016 proposed rule based on this comment. We acknowledge that the criteria have been and will be applied on a substance-by-substance basis, given the risks and benefits that may be presented by a particular substance. The Agency believes some measure of flexibility is necessary for FDA to evaluate the nominated bulk drug substances. We have applied and will continue to apply the criteria consistently, weighing them as appropriate based on the nature of the substance and proposed use, among other things. FDA also notes that its application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and also is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not applying the criteria correctly in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 3) One commenter objected to the fourth criterion FDA proposed in the 2016 proposed rule: ''Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.'' The commenter explained that current use is more relevant than historical use.

(Response 3) We disagree that FDA should not consider historical use. Further, we note that consideration of current use is encompassed in the historical use criterion. Regarding the criteria used to determine whether a bulk drug substance should be placed on the 503A Bulks List, section 503A(c)(2) of the FD&C Act specifies that the criteria shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify. We are, therefore, required by statute to consider the historical use of a bulk drug substance. As we explained in the 2016 proposed rule, the Agency is considering how widespread the use of a bulk drug substance has been, as well as references in peer-reviewed medical literature, as part of the evaluation of the historical use.

(Comment 4) One commenter objected to FDA's consideration of the historical use criterion, noting that FDA has not been giving this factor adequate weight. This commenter suggested that, instead of applying the criterion as proposed, FDA should recommend a bulk drug substance for the 503A Bulks List if it has historically been in significant use by a particular specialty or community of physicians unless there is reliable evidence that the ingredient presents unacceptable sterility concerns or potential for adverse reactions.

(Response 4) As noted above, FDA is statutorily required to consider historical use when evaluating the nominated bulk drug substances, and the Agency has been doing so. To the extent information pertaining to historical use has been available, it has been discussed at length in each of the reviews underlying FDA's recommendations to the PCAC and its proposals in the 2016 proposed rule. As noted above, each criterion may weigh differently in the context of the risks and benefits presented by a particular bulk drug substance, and historical use may weigh more heavily in some cases than others. As also stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not giving the historical use criterion adequate weight in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance from the 503A Bulks List. We decline to adopt the commenter's suggestion to consider historical use as dispositive in certain cases, as we believe doing so would give disproportionate weight to the historical use criterion and would not give adequate consideration to a substance's physical and chemical characterization, safety, or effectiveness.

(Comment 5) Some commenters objected to FDA's consideration of the availability of approved drug products or drug products that conform to an over-the-counter (OTC) monograph to treat the same condition as the proposed bulk drug substance, and proposed that these alternatives not weigh against inclusion of the substance on the 503A Bulks List. The commenters noted that drug products are compounded because the drugs already available are not appropriate or effective for individual patients. Further, the commenters opposed the consideration of alternative therapies because they assert FDA has failed to consider the side effects of FDA-approved products, and any concern that use of compounded drugs could delay use of approved products is baseless. One of the commenters suggested that the approved alternatives should only be considered where the approved medication leads to a complete cure or remission of illness or otherwise fully addresses the purpose intended for the compounded drug product, and there is no other reason a compounded drug product containing the nominated bulk drug substance should be available.

(Response 5) We disagree with this comment and believe that the existence of FDA-approved drug products or drug products that conform to an OTC monograph may be relevant in the evaluation of particular bulk drug substances. However, the existence of alternative therapies is not one of the four criteria FDA is using to evaluate nominated bulk drug substances, nor is the availability of approved alternatives dispositive when considering whether to add a substance to the list. Rather, as explained in the 2016 proposed rule, we consider the existence of FDA-approved or OTC-monograph drug products relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. Therefore, we find no reason to exclude consideration of the existence of FDA-approved or OTC monograph drug products where relevant.

Regarding the comment that FDA has not adequately considered the side effects of alternative therapies, we disagree and have considered the side effects of alternative therapies as part of the safety criterion where information is available and relevant. We note, however, that data comparing the safety profiles of compounded drug products with approved drug products are generally not available. In fact, in many cases, there are minimal data available concerning the safety, including side effects, of compounded drugs. The absence of information does not mean that safety risks do not exist. In contrast, approved drug products have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the benefits of the drug product for the approved conditions of use have been found to outweigh the risks. Similarly, regarding effectiveness, often there are minimal data supporting the effectiveness of a compounded drug product, and it may be preferable for a patient to use a drug product with side effects when that drug product has been proven to be effective. Even if a compounded drug product has fewer side effects than an FDA-

approved or OTC monograph drug product, if it does not treat the condition at issue, it may be of no or limited benefit to the patient.

Regarding the comment that approved alternatives should only be considered when there is evidence that the FDA-approved drug product or OTC monograph product fully addresses patients' needs, we disagree. While not one of the four criteria, as described in the 2016 proposed rule and reflected in reviews completed and presented to the PCAC, under certain circumstances, the existence of an approved drug product or OTC monograph product to treat the condition, even where the product may not fully address patients' needs, is relevant to FDA's evaluation of one or more of the four criteria. For example, in considering the effectiveness criterion, the existence of an approved drug product or OTC monograph product may weigh against placing a substance on the 503A Bulks List when the condition to be treated is very serious or life threatening because of the serious consequences that could result from use of an ineffective or less effective treatment alternative (2016 proposed rule, 81 FR 91071 at 91075.) Likewise, in considering the safety criterion, the existence of an approved drug product or OTC monograph product likely would weigh against placing a substance on the 503A Bulks List when the toxicity of the substance appears to be significant, or other safety concerns are associated with the use of the substance (id.).

Further, we note that, as stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not adequately considering the side effects of FDA-approved products in any particular case, the Agency will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 6) One commenter proposes that a substance should be added to the 503A Bulks List if the Center for Food Safety and Applied Nutrition (CFSAN) has determined the substance is generally recognized as safe (GRAS).[1]

(Response 6) We disagree. GRAS determinations for food are made under food safety standards and thus are not dispositive when considering the use of a substance as an active ingredient in a compounded drug product. A substance that is safe when used as a food might not be safe as an active ingredient in a drug product, for example, when used for a route of administration other than oral. Moreover, such a GRAS determination does not indicate that a substance would have any effectiveness for a particular proposed use when used in a compounded drug product. We note, however, that FDA has considered CFSAN's GRAS notices and their implications in reviews completed to date where relevant, for example, in our review of safety or physical and chemical properties.

As stated above, FDA's application of the criteria to particular substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not adequately considering the GRAS determination of a substance in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 7) One comment objected to FDA's consideration of the seriousness of the condition the drug product compounded with the nominated bulk drug substance is proposed to treat. In the 2016 proposed rule, FDA proposed to weigh the effectiveness criterion more heavily when the bulk drug substance was proposed to treat a serious or life-threatening disease, and to give the safety criterion more weight when the substance was proposed for treatment of a less serious disease. The commenter asserted that there is no rational basis for such a standard.

(Response 7) We disagree with the comment. As we explain in the 2016 proposed rule, when a bulk drug substance is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy. When evaluating a bulk drug substance that is proposed for the treatment of a less serious illness, FDA will generally be more concerned about the safety of the substance than about its effectiveness. For these reasons, we find no reason to discontinue consideration of the seriousness of the condition the bulk drug substance is nominated to treat.

(Comment 8) One comment objected to the process FDA used to implement the criteria, noting that FDA was required to consult with the PCAC and obtain stakeholder input through notice and comment rulemaking before going forward with substance evaluations using the proposed criteria. The commenter asserts that there was no formal debate or discussion of the criteria with the PCAC.

(Response 8) We acknowledge that FDA began considering the proposed criteria and presenting recommendations to the PCAC before the criteria were finalized in this rulemaking. We believe that the criteria could not have been fully vetted and considered, by both the PCAC and USP, as well as commenters to the 2016 proposed rule, without illustration of how those criteria would apply in practice to evaluation of nominated bulk drug substances. As discussed in this rulemaking, FDA has considered the comments received on the proposed criteria and has found no basis to change those criteria based on the comments received.

We disagree, however, with the comment asserting that there was no formal debate or discussion of the criteria with the PCAC. As discussed in the 2016 proposed rule, FDA presented the criteria to the PCAC and discussed the criteria with the PCAC at its February 23, 2015, meeting (Ref. 2). The public had the opportunity to attend and speak at the PCAC meeting at which these criteria were discussed. The public also had the opportunity to review the transcript of the discussion that took place at the PCAC meeting, both prior to the publication of the proposed rule via publication of the transcript on the FDA website and through the docket for the proposed rule, where the transcript was included as a reference. FDA also consulted with USP regarding the criteria, and USP agreed with the proposed criteria (Refs. 3 and 4).

2. Application of the Proposed Criteria to Date

(Comment 9) Some commenters objected to the proposed criteria as being underinclusive of the factors FDA has been applying in practice in its evaluations of the nominated bulk drug substances. Specifically, several comments stated that FDA's application of the proposed criteria has been skewed by inappropriate consideration of the availability of an investigational new drug (IND) application pathway,

[1] Under sections 201(s) and 409 of the FD&C Act (21 U.S.C. 321(s) and 348), any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excepted from the definition of a food additive. For more information, see *https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/*.

which should not be relevant to FDA's recommendation of whether to include a particular bulk drug substance on the 503A Bulks List.

(Response 9) We disagree with the comment that the proposed criteria are underinclusive of the factors FDA has been applying in practice. While the PCAC presentations and discussions have encompassed some information of interest that is not directly related to the four criteria, such as the differences in regulatory standards between dietary supplements and drug products, or general information about compounding facilities, that information was not the basis of FDA's recommendations or decisions with respect to the bulk drug substances. Rather, in each of FDA's reviews (included in the record for the 2016 proposed rule), our recommendations have been derived directly from consideration and balancing of the four criteria: (1) Physical and chemical characterization of the substance; (2) any safety issues raised by the use of the substance in compounded drug products; (3) available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and (4) historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

The option of making a substance available through an IND application has been discussed by the PCAC and addressed in some reviews to help inform the public of ways in which the drug can be further studied and used to treat patients. In no review to date, however, has the option of pursuing an IND been a basis in FDA's proposals to include, or not to include, a nominated bulk drug substance on the 503A Bulks List. For each substance evaluated to date, FDA has made its proposals based on the four criteria described above, without regard to the existence of, or option to pursue, an IND. We note that FDA can make recommendations to the PCAC, but the Agency cannot control the content of the PCAC's discussions or its advice. FDA takes the PCAC's discussions and advice, including the basis for any advice, into account when considering whether to propose a substance be placed on the 503A Bulks List.

As stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has inappropriately considered the availability of an IND in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 10) One comment asserted that FDA's application of criteria to evaluate bulk drug substances to date has been inconsistent. For example, according to the commenter, in some cases FDA and the PCAC recommended to include a bulk drug substance on the 503A Bulks List so there is an alternative to approved products, but in other cases, FDA and the PCAC recommended to not include a substance on the list because there is already an approved product available.

(Response 10) We disagree with this comment. As we noted above, the criteria are applied on a substance-by-substance basis, and a criterion that may be weighed heavily for one bulk drug substance might be weighed differently for another, given the risks and benefits that may be presented by a particular substance. We have applied, and will continue to apply, the criteria consistently, weighing them as appropriate based on the nature of the substance and proposed use, among other things. Also as stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP and is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has not applied the criteria correctly in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 11) One comment objected to the level of evidence of clinical effectiveness and toxicology FDA has been considering in its application of the proposed criteria. According to the comment, these high standards of evidence are unreasonable and change fundamental standards of practice. The comment asserts that FDA appears to be requiring studies that can survive any criticism and is ignoring the role of physician decisions based on clinical experience.

(Response 11) We disagree with the comment. As stated in the 2016 proposed rule, FDA recognizes that it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. We note that the evidence that has supported FDA's recommendations to place particular substances on the 503A Bulks List to date has not been of the type or quality that is ordinarily required and evaluated as part of the drug approval process. We further note that we considered the input of physicians and their clinical experience to the extent that information is provided to the Agency, including that provided during PCAC meetings. We find no reason to reduce the amount of evidence FDA has considered necessary to support a recommendation to include a bulk drug substance on the 503A Bulks List and believe that doing so would not be in the interest of public health.

(Comment 12) One comment asserted that application of the criteria to date has been too narrow in its application to a particular proposed use.

(Response 12) We disagree and believe that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance. We acknowledge that inclusion of a substance on the 503A Bulks List is not limited to a specific use. However, for evaluation purposes, FDA finds it necessary to consider the criteria, particularly the effectiveness criterion, in the context of a specific proposed use or uses. Given the number of substances nominated for inclusion on the list, it would not be possible for FDA to consider all possible uses for a compounded drug product that includes the nominated substance. Therefore, we find it reasonable to rely on information from the interested parties who nominated the bulk drug substances to identify the proposed uses, and for FDA to evaluate the substance in the context of those uses.

Nevertheless, as indicated in the 2016 proposed rule, when FDA is aware of another use that may be relevant to its evaluation of a substance for the 503A Bulks List, such as when a use other than that for which it was nominated is widespread, FDA may consider that use in its discretion.

As discussed in the 2016 proposed rule, FDA has opened a docket through which interested individuals may nominate additional bulk drug substances or provide additional information about substances already nominated with sufficient information for the 503A Bulks List (see Docket No. FDA–2015–N–3534). If an interested party believes that the nominations for a particular substance did not include a proposed use that it would like to be reviewed, and that substance has not yet been addressed in an NPRM, additional

information or nominations may be provided through that docket.

(Comment 13) One comment asserted that application of the criteria to date has given undue weight to possible side effects or safety concerns related to use of compounded drug products, which are often speculative.

(Response 13) We disagree with the comment. FDA's reviews of nominated substances to date have appropriately balanced the safety criterion with the other three criteria, and FDA has applied its scientific judgment to identify side effects or safety concerns based on available data and information. As stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has inappropriately considered safety information related to compounded drug products in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 14) One comment objected to statements made during PCAC meetings indicating concern that, if a bulk drug substance is placed on the list, drug products compounded with that substance could be marketed with any claims. The comment notes that marketing a drug product for unsubstantiated claims is illegal, and if FDA and PCAC are concerned that this is happening, appropriate action and education should be undertaken. The commenter asserts that the possibility of misleading marketing should not be considered when determining whether to include a bulk drug substance on the 503A Bulks List.

(Response 14) We did not consider the possibility of misleading marketing when determining whether to include a bulk drug substance on the 503A Bulks List. Under section 502(bb) of the FD&C Act, a compounded drug will be deemed misbranded if the advertising or promotion of such compounded drug is ''false or misleading in any particular.'' In addition, under section 502(a) of the FD&C Act, a drug will be deemed misbranded if its labeling is ''false or misleading in any particular.'' However, the existence of false or misleading advertising is not one of the four criteria considered when evaluating a nominated substance for inclusion on the 503A Bulks List.

3. FDA's Proposals on Specific Substances

(Comment 15) One comment requests that the listing of NAG codified at § 216.23(a) (21 CFR 216.23(a)) not be limited to topical use only, and instead, to allow use of that substance by any route of administration. The comment notes that one of the nominations for that bulk drug substance was not limited to topical use.

(Response 15) We disagree that the listing for NAG in the codified should be expanded beyond topical use. As we explained in the **Federal Register** of July 2, 2014 (79 FR 37747 at 37748 (July 2014 Request for Nominations)), which detailed the type of information to be provided with nominations, FDA only intended to review nominations that were supported with adequate data and information. Doing so has allowed FDA to focus its limited resources on the nominated uses and routes of administration for which nominators have provided the most support. Also, as indicated in the July 2014 Request for Nominations, the Agency reviewed information for multiple nominations of the same substance collectively (79 FR 37747 at 37749).

None of the nominations for NAG proposed or provided information that would support administration of NAG by any route of administration other than topical. The nomination from the International Academy of Compounding Pharmacists mentioned in the comment did not specify a proposed use or route of administration. Rather, the nomination stated only that ''[t]he very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription.'' (Ref. 5.) Taken alone, this nomination did not provide adequate support to allow FDA to evaluate the nominated substance (for topical or other routes of administration), and it was only considered collectively with the other nominations for NAG for topical use. As noted in the 2016 proposed rule, individuals and organizations may petition FDA under 21 CFR 10.30 to amend the list, including to request that the Agency evaluate NAG for routes of administration other than topical. See Response 31 for further discussion of the petition process.

(Comment 16) Some comments object to the exclusion of oxitriptan from the 503A Bulks List and request that oxitriptan be included on the list codified at § 216.23(a). The comments state that oxitriptan is widely sold as a dietary supplement and that it has an extensive safety record through its long history of use as a dietary supplement, which they believe should be given more weight. The comments assert that patients benefit from a relationship with their prescriber and pharmacist that is not available in the dietary supplement context because dietary supplements are purchased over the counter. According to one of the commenters, there is no evidence of any risk that oxitriptan would have the same side effects as other medications used to treat depression, and the mechanism of action of oxitriptan is demonstrably different from that of approved therapies. The comment asserts that oxitriptan's safety profile is significantly better than that of approved products. One comment also asserts that oxitriptan has been shown to be effective in the treatment of a variety of conditions, including depression and insomnia.

(Response 16) We have considered the comments and the references cited therein (Refs. 6 to 9), and find no reasoning or data that cause FDA to change its evaluation not to include this substance on the 503A Bulks List. As noted above, the availability of a substance as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are intended for oral ingestion only, are not intended to be used to treat diseases, and therefore, are subject to a different legal and regulatory scheme than drug products. Section 503A addresses compounded drug products only. We acknowledge that FDA's reviews and PCAC meetings included discussions about the availability of dietary supplements with dietary ingredients that were the same or similar to the nominated bulk drug substances. As noted in prior PCAC discussions, FDA's proposals in this context do not impact a substance's availability as a dietary supplement.

Regarding the argument that there is no evidence of any risk that oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) would have the same side effects as other medications used to treat depression, as previously stated in FDA's review (Ref. 5), there is a dearth of reliable scientific data regarding the safety of oxitriptan. We found no data indicating that the use of oxitriptan for depression would be free of the same side effects as other medications used to treat depression, and no reliable scientific data were provided in the comments received on the proposed rule to support this assertion.

Regarding the argument that the mechanism of action of oxitriptan is demonstrably different from that of approved therapies, as previously stated in FDA's review, the psychoactive action of oxitriptan is related to increased production of serotonin in central nervous system tissue (id). Based on this mechanism of action, oxitriptan, particularly with concomitant use of antidepressant drug products, could result in serotonin syndrome, a life-threatening drug interaction, and cases that are likely to be serotonin syndrome have been reported with the use of oxitriptan as a dietary supplement (Ref. 10). In fact, one source cited by a commenter warns against taking oxitriptan with certain approved antidepressants because both increase the brain chemical serotonin and taking both ''might increase serotonin too much and cause serious side effects including heart problems, shivering, and anxiety'' (Ref. 7).

Regarding the argument that oxitriptan's safety profile is significantly better than that of approved products, we disagree. As explained in Response 5, data comparing the safety profiles of compounded drug products with approved drug products are generally not available, and we do not have any such comparative data here. As stated above, the absence of information does not mean that safety risks do not exist. In contrast, approved drug products have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the benefits of the drug product for the approved conditions of use have been found to outweigh the risks.

Regarding the argument that oxitriptan has been shown to be effective for the treatment of a number of conditions, including depression and insomnia, similarly, the comments provided no reliable scientific data that would cause FDA to change its evaluation of oxitriptan, which balanced the available data on effectiveness with the other three criteria. As stated in the 2016 proposed rule, data supporting the drug's effectiveness for depression and insomnia are limited, and there are no data to support the effectiveness of the long-term use of oxitriptan to treat depression. FDA's conclusion in the 2016 proposed rule regarding the effectiveness of oxitriptan for insomnia and depression was based on FDA's consideration of more recent and comprehensive data than that provided by the commenters, and the information provided by the commenters does not alter that conclusion. We also note that one source cited by a commenter stated that there is insufficient evidence to rate the effectiveness of oxitriptan for insomnia (Ref. 7).

In sum, we have reviewed the scientific references and considered the reasoning set forth in the comments, and they do not change FDA's analysis of oxitriptan as stated in our review (Ref. 5) or our conclusion that it should not appear on the 503A Bulks List.

(Comment 17) Some comments object to the exclusion of piracetam from the 503A Bulks List and request that piracetam be included on the list codified at § 216.23(a). The comments note that FDA has recognized that there is not a significant safety risk related to the use of piracetam. They assert that the recommendation to exclude piracetam from the 503A Bulks List was based on a presumption that piracetam could be obtained through an IND, which was not a proper consideration. One comment provided data about the effectiveness of piracetam for short-term cognitive performance (Ref. 11) and the safety of its administration in high doses to patients with acute stroke (Ref. 12).

(Response 17) We have considered the comments and references cited therein and find no reasoning or data that cause FDA to change its evaluation not to include this substance on the 503A Bulks List. Regarding the safety of piracetam, we note that while our review of piracetam indicated that doses of less than 8 grams per day [2] appear to be unlikely to cause serious adverse reactions or drug interactions, the review also described safety concerns associated with certain patient populations and certain concomitant medications (Ref. 13). Piracetam is not recommended for patients with severe renal impairment because clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency. Piracetam is also not recommended for those taking concomitant anticoagulants because piracetam reduces platelet function, interferes with clotting factors, and prolongs bleeding time at certain doses. We also note that, in evaluating piracetam, we considered the three other criteria in addition to the safety of piracetam.

Although it is well characterized chemically and physically and has been used in compounded drug products for approximately 40 years, as stated in its review, FDA is concerned about the effectiveness of piracetam (id.). The available data do not show a clear benefit associated with the use of piracetam (id.). Numerous studies of piracetam have been conducted, and all but a few were designed poorly or used inappropriate statistical methods to support conclusions that piracetam is effective as a treatment for the studied condition (id.). The publications that suggest piracetam is effective for treating cognitive impairment, acute vertigo, or stroke are inconsistent, and there are also publications that conclude that piracetam is ineffective for treating these same conditions (id.). We were able to identify a single, well-designed and executed study of piracetam, which showed that it is ineffective for the treatment of cognitive impairment (Ref. 14).

The two scientific articles referenced in the comments, one of which is discussed in FDA's evaluation of piracetam (Ref. 11), and the other of which addressed the safety of high doses of piracetam when used as a treatment for acute stroke (Ref. 12), do not address FDA's concerns regarding the lack of data supporting its effectiveness in treating serious and life-threatening conditions such as stroke. For the reasons set forth above, neither the scientific references nor the reasoning set forth in the comments provide a basis for FDA to change its analysis of piracetam according to the four criteria (Ref. 13), or FDA's ultimate conclusion that piracetam should not appear on the 503A Bulks List.

Finally, we acknowledge that the possibility of pursuing an IND application for piracetam was discussed at the PCAC meeting (Ref. 15) to inform the public of a pathway to study and access piracetam. FDA did not consider the availability of an IND in its review of piracetam under the four criteria, however (Ref. 13). As FDA explained in its review, based on the absence of a clear benefit associated with piracetam, the seriousness of the conditions for which piracetam was proposed for use, and the availability of safe and effective medications for many of these uses that have undergone greater scientific scrutiny (id.), FDA proposed piracetam not be placed on the 503A Bulks List.

(Comment 18) One comment objects to the exclusion of silver protein mild from the 503A Bulks List and requests that silver protein mild be included on the list codified at § 216.23(a). The comment states that silver protein mild is well characterized physically and chemically, has a long history of use, is relatively nontoxic, and side effects are only rarely reported.

(Response 18) We have considered the comment and find no reasoning or data therein that cause FDA to change its

[2] Note that FDA's review stated that doses of less than ''8 kg/day'' appear unlikely to cause serious adverse reactions or drug interactions, but ''kg'' was a typographical error. That statement of the review should have been ''8 g/day.''

evaluation not to include this substance on the 503A Bulks List. As stated in the 2016 proposed rule, silver protein mild is not well-characterized, and the term ''silver protein mild'' can refer to a variety of different drug products. FDA is also concerned about the safety of silver protein mild, which can cause argyria (a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs) (Ref. 13). Despite the commenter's characterization of the substance as relatively nontoxic, FDA remains concerned that chronic use of silver protein mild may result in permanent discoloration of the conjunctiva, cornea, and/or lens (id.). As for the commenter's characterization that the side effects are rarely reported, we note that the use of silver protein mild declined precipitously after the introduction of FDA-approved ocular anti-infectives. As described in FDA's review, numerous articles and books published when silver protein mild was more commonly used described deposits of silver in the conjunctiva, lacrimal sac, cornea, and lens following administration (id.).

We also note that there is no reliable evidence that silver protein mild would be effective for the proposed use. It has been studied in two controlled studies. In one study, silver protein mild was found to be numerically, although not statistically, inferior to having no treatment at all. In the second study, silver protein mild was found to be inferior to povidone iodine, which is an FDA-approved drug product (id.). While silver protein mild does have a long history of use, dating back to the early 1900s, as noted above, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives (id.).

The reasoning set forth in the comment does not address FDA's concerns about the characterization, safety, or effectiveness of silver protein mild, and does not change FDA's conclusion that silver protein mild should not appear on the 503A Bulks List.

(Comment 19) Some comments object to the exclusion of tranilast from the 503A Bulks List and request that tranilast be included on the codified list at § 216.23(a). The commenters note that FDA's proposal not to include tranilast is contrary to the advice of the PCAC. They assert that FDA's view is based on a faulty understanding of the increased bilirubin observed in clinical trials and note that the proposed topical dosage is well below that used in those trials. One comment described anecdotal reports that the topical use of tranilast has been effective in the treatment of keloids and hypertrophic scars. Another comment asserted that tranilast has been available in Japan for over 30 years, apparently without detrimental effects.

(Response 19) We have considered the comments and decline to include tranilast on the 503A Bulks List. As stated in the 2016 proposed rule, FDA has serious concerns about the safety of tranilast when administered orally, and there is insufficient information about the systemic absorption of topical tranilast formulations to determine whether topical administration of the drug product presents the same safety concerns (81 FR 91071 at 91079). No new data about the use of tranilast were provided in the comments; rather, the comments provided only anecdotal reports about the use of tranilast and further discussion of the same data presented to the PCAC, which FDA considered prior to publishing the 2016 proposed rule. The reasoning in the comments did not sufficiently address FDA's safety concerns regarding the use of this substance.

We acknowledge that the PCAC recommended including tranilast on the 503A Bulks List with a restriction to topical use. However, advisory committee recommendations are not binding on FDA. Rather, FDA considers the PCAC's advice but makes an independent judgment regarding whether particular substances should appear on the 503A Bulks List. As we explained in our supplemental review of tranilast (Ref. 16) and the 2016 proposed rule, the government-approved Japanese tranilast product label provided evidence of teratogenicity in animals and contraindicated the use of tranilast in pregnant women or women who may become pregnant. We did not find that the risk of prescribing a potential teratogen to women who may be or may become pregnant was outweighed by the potential benefit of treating scar tissue. Therefore, FDA continues to believe that the criteria weigh against placing tranilast on the 503A Bulks List.

Regarding the commenter's statements about the effectiveness of tranilast for keloids and hypertrophic scarring, scientific data supporting effectiveness for those uses are lacking. While there is some evidence that tranilast may be effective for allergic disorders, evidence of effectiveness for those other uses is either not available or inconclusive (Refs. 5 and 16).

(Comment 20) One comment objected to the rejection of substances that are dietary supplements from the 503A Bulks List. The commenter states that by rejecting these substances from the list, FDA is forcing consumers to use products that are subject to less quality oversight and lack physician supervision. The commenter proposes that dietary supplements only be rejected for proven safety concerns.

(Response 20) As stated in Response 16, a substance's availability as a dietary ingredient or supplement is not a criterion when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are intended for oral ingestion only, and are not intended to be used to treat diseases, and therefore, are subject to a different legal and regulatory scheme than drug products. Section 503A of the FD&C Act addresses compounded drug products only. To the extent FDA's reviews and PCAC meetings included discussions about the availability of dietary supplements with dietary ingredients that were the same or similar to the nominated bulk drug substances, we note that FDA's proposals in this context do not impact a substance's availability as a dietary supplement.

Regarding the comment about the lack of quality oversight for dietary supplements, we note that dietary supplement manufacturers are required to comply with FDA's Current Good Manufacturing Practice regulations for dietary substances and are subject to inspection by FDA (21 CFR part 111). Regarding physician supervision, we note that physicians may recommend dietary supplements to their patients regardless of whether the substance appears on the 503A Bulks List.

4. Dietary Supplement Monographs and Other Monographs

(Comment 21) Some commenters objected to FDA's interpretation, as stated in the 2016 proposed rule, that dietary supplement monographs are not ''applicable monographs'' for purposes of determining which substances may be included in compounded drug products under section 503A(b)(1)(A)(i)(I) of the FD&C Act. They note that physicians may prescribe dietary supplements. They also state that in a ''2014 guidance,'' [3] FDA said that dietary supplement monographs were ''applicable monographs'' under section 503A, and that change in policy has not been explained.

(Response 21) We disagree that dietary supplement monographs should be considered ''applicable monographs'' for purposes of section 503A of the FD&C Act. As stated in the 2016 proposed rule, section 503A sets forth conditions that must be met for a

[3] One comment appears to refer to the July 2014 Request for Nominations as ''guidance'' on this topic.

compounded drug product to qualify for certain exemptions from the FD&C Act. Among other conditions, section 503A(b)(1)(A)(i) of the FD&C Act requires that a bulk drug substance used in a compounded drug product meet one of the following criteria: (1) Comply with the standards of an applicable USP or NF monograph, if one exists; (2) be a component of an FDA-approved human drug product, if a monograph does not exist; or (3) be on a list of bulk drug substances that may be used for compounding, to be developed by FDA through regulation. FDA has interpreted the term ''an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph'' to refer to official drug substance monographs. Therefore, a substance that is the subject of a dietary supplement monograph, but not a drug substance monograph, may only be compounded if the substance is a component of an FDA-approved drug product or is on the FDA's list of bulk drug substances that may be used for compounding.

This interpretation is both legally supportable and in the best interest of the public health. Under the FD&C Act, drugs and dietary supplements are different product categories that are subject to different regulatory schemes. Section 503A, the key statutory provision for this rulemaking, concerns pharmacy compounding of drug products, not dietary supplements. It states that a drug product may be compounded under section 503A(a) of the FD&C Act if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that comply with the standards of an *applicable United States Pharmacopoeia or National Formulary monograph,* if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding (emphasis added). (See section 503A(b)(1) of the FD&C Act.)

Accordingly, it is reasonable to interpret the phrase ''applicable United States Pharmacopoeia monograph'' in this statutory provision as a reference to USP *drug* monographs, not USP dietary supplement monographs. Moreover, adopting the alternative interpretation urged by the comment—*i.e.,* that ''applicable'' USP monographs include dietary supplement USP monographs—would not be in the best interest of the public health. USP monographs for dietary supplements can differ in significant ways from USP monographs for drugs because of the differences between dietary supplements and drug products. For example, dietary supplements are intended for ingestion only, and the standards contained in the USP dietary supplement monographs are likewise intended for dietary supplements that will be ingested; the standards are not appropriate for use in compounding drug products that may have different routes of administration (*e.g.,* intravenous, intramuscular, topical). In addition, the USP limits for elemental impurities are different for drugs and dietary supplements: There are limits specified in USP General Chapters for many more elemental contaminants for drugs than there are for dietary supplements. Furthermore, the bioburden allowable for dietary supplements is considerably higher than that allowed for drug substances. Relying on the standards of a dietary supplement monograph for a substance that will be used in compounding drug products could therefore put patients at risk.

We disagree with the commenter's statement that a 2014 guidance stated that dietary supplement monographs were ''applicable monographs'' under section 503A of the FD&C Act. FDA is unaware of any Agency statements that support that view, including the July 2014 Request for Nominations.

(Comment 22) One comment asserted that the Homeopathic Pharmacopeia of the United States (HPUS) homeopathic monographs and other types of monographs should be considered ''applicable monographs'' under section 503A(b)(1)(A)(i)(I) of the FD&C Act, making substances that are the subject of such monographs eligible for use in compounding. The comment asserted that the Drug Quality and Security Act (DQSA) (Pub. L. 113–54) gives FDA authority to designate sources other than USP or NF monographs as ''applicable monographs.'' The comment also noted that the FD&C Act recognizes the HPUS as ''official'' in 21 U.S.C. 358(b), and in the definitions at 21 U.S.C. 321, the FD&C Act defines ''drug'' to include articles recognized in the HPUS.

(Response 22) We disagree that HPUS homeopathic monographs and other types of monographs should be considered ''applicable monographs'' under section 503A. The provisions of DQSA cited in the comment do not apply to section 503A of the FD&C Act. Rather, the language of section 503A explicitly applies only to applicable USP or NF monographs. Therefore, we decline to consider HPUS or other types of monographs to be ''applicable monographs'' under section 503A(b)(1)(A)(i)(I) of the FD&C Act.

(Comment 23) One commenter asserted that incorporating the statements about FDA's interpretation of ''applicable monographs'' from the Interim Policy Guidance effectively and improperly converts that guidance document to rulemaking. The commenter pointed out that regulations cannot be issued through guidance documents and stated that the guidance should be rescinded.

(Response 23) We disagree with this comment. Describing an interpretation of the applicable statute in both a guidance document and in a preamble to a proposed rule does not ''convert'' the guidance document to a rulemaking and has no impact on the status of the guidance. The guidance document was issued in accordance with our ''Good guidance practices'' regulation (21 CFR 10.115).

5. Conflict of Interest

(Comment 24) One comment stated that FDA should consider its ''conflict of interest'' arising from the Agency's receipt of funds under the Prescription Drug User Fee Act (PDUFA) related to new drug applications (NDAs). According to the commenter, these funds cause FDA to be biased in favor of approved products.

(Response 24) We disagree with this comment. It is unclear what action the commenter was suggesting that FDA take to address this perceived ''conflict of interest.'' We note that the receipt of PDUFA fees related to NDAs has not affected FDA's ability to be impartial when evaluating bulk drug substances for inclusion on the 503A Bulks List. The Agency believes that compounded drugs can play a critical role for patients whose medical needs cannot be met by an approved drug.

Moreover, FDA's recommendations on particular bulk drug substances are subject to discussion with the PCAC and USP, and are the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes its recommendations are biased in any particular cases, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

6. Qualifiers for Use of Substances on the 503A Bulks List

(Comment 25) One comment requested that FDA allow inclusion of bulk drug substances on the list with certain qualifiers or limited uses, such as dose or dosage form. The comment stated that such qualifiers will give FDA greater leeway to add bulk drug substances to the list, which will benefit patients.

(Response 25) We agree that in some limited cases, it may be appropriate to place bulk drug substances on the 503A

Bulks List subject to a restriction on use, such as the route of administration. For example, several of the substances that are being added to the list in this rulemaking are restricted to topical use only. For the substances we are not including on the list in this rulemaking, we found no relevant qualifiers on the compounded drug product, such as route of administration, that would have justified inclusion of the substances on the list.

7. Process Issues Related to FDA's Evaluation of Nominated Bulk Drug Substances and PCAC Consultations

(Comment 26) One comment raised concerns about the composition of the PCAC. The commenter asserted that the professions most familiar with compounded drug products are not represented on the PCAC, and neither FDA nor the PCAC has the necessary expertise to make judgments on the nominated bulk drug substances. In particular, according to the commenter, naturopaths need to be consulted, and a counterbalance to the representation by Public Citizen and the Pew Charitable Trusts is needed on the committee. The comment stated that PCAC members may have conflicts of interest.

(Response 26) We disagree with the comment. Of the current PCAC members, seven are pharmacists, and five are physicians. Twelve committee members have experience related to drug compounding, including experience in the preparation, prescribing, and use of compounded medications, as well as compounding-related research activities. In accordance with section 503A of the FD&C Act, one member is a representative from USP, and one member is a representative from the National Association of Boards of Pharmacy.

Industry participated in the selection of two additional committee members—one from the pharmaceutical manufacturing industry and one from the compounding industry. Additionally, a consortium of consumer advocacy representatives participated in the selection of a consumer representative.

More than 100 names were submitted to the Agency in response to the January 13, 2014, **Federal Register** notices requesting nominations.[4] (79 FR 2177; 79 FR 2178; 79 FR 2179.) In addition, FDA identified qualified candidates from its own pool of special government employees. The selection process of candidates that were not designated representatives of particular groups included evaluation for conflicts of interest as required by 21 CFR 14.80, and for the relevancy of their qualifications for the purpose of the committee. Candidates with actual or potential conflicts of interest in matters that would come before the committee were eliminated from consideration. For example, for those candidates not representing a particular group, FDA reviewed whether the candidate owned a compounding pharmacy, consulted for the compounding industry, or supplied bulk drug substances for compounding, because those activities would likely raise a financial interest that could be affected by the matters expected to come before the committee.

In general, members are invited to serve for overlapping terms of up to 4 years. As it has to date, the Agency will consider future nominations for membership and strive to select members with robust and relevant experience and expertise related to drug compounding.

Nominations may be submitted to the Advisory Committee Membership Portal at any time and submitted nominations will be considered as vacancies occur. See *https://www.accessdata.fda.gov/scripts/FACTRSPortal/FACTRS/index.cfm.* See *https://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/ApplyingforMembership/default.htm* for more information on the nomination procedure.

(Comment 27) One comment asserted that FDA has ''unfairly screen[ed]'' the evidence provided by nominators to the PCAC, has ''misrepresented'' the availability of other routes of approval of drug products compounded with the nominated bulk drug substance, and has ''manipulated'' the PCAC into rejecting certain nominated substances. The commenter stated that FDA appeared to be ''cherry-picking'' studies only to show negative data, and was not scrutinizing studies that showed safety concerns with the use of the bulk drug substance in the same way that it has scrutinized studies the nominators put forward to show effectiveness.

(Response 27) We disagree with this comment. As stated above, FDA is determining whether to place a substance on the list after weighing available data and information in light of the four criteria set forth in this rulemaking and considering feedback from PCAC, USP, and the public. FDA considers publicly available studies that are relevant to the evaluation criteria, regardless of the source of those studies.

As stated above, if members of the public believe FDA is not giving adequate weight to certain studies, or is otherwise misrepresenting information presented to the PCAC in any particular case, they are encouraged to submit a comment to the docket for the NPRM in which the substance at issue is addressed. Nominators and the public are also invited to present at PCAC meetings where they have an opportunity to discuss their interpretation of the relevant studies and address the PCAC regarding each substance considered. FDA will consider all feedback received before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 28) Some comments stated that nominators were not being given equal time with FDA to make presentations to the PCAC, and instead were limited to 10-minute presentations. Commenters asserted that this imbalance is unfair and has resulted in skewed decision making by the PCAC. Commenters also asserted that nominators were given insufficient notice of PCAC meetings and did not have adequate time to prepare.

(Response 28) We acknowledge that FDA presentations have been allotted more time than those by nominators, which we believe is appropriate given that FDA is tasked with developing the 503A Bulks List and is necessary for FDA to present fully on the reviews of the bulk drug substances.

Regarding notice of PCAC meetings, FDA has notified the public at least 20 days prior to PCAC meetings, and the Agency strives to give notice further in advance where possible. However, further advance notice is not always possible due to the need to coordinate various logistical issues.

(Comment 29) Some commenters noted that it was not possible for nominators to provide the information FDA requested in its July 2014 Request for Nominations for the list of bulk drug substances that can be compounded under section 503A of the FD&C Act for two reasons. First, commenters stated there is a gap between the stated criteria and how FDA is applying the criteria, and therefore, nominators did not have sufficient notice of what information would be needed for FDA's decision making. Second, commenters asserted that it is not possible to provide the information FDA required for a nomination because decisions about how a compounded drug is used are at the discretion of the physician.

(Response 29) We disagree with this comment. As noted previously, FDA is applying the four criteria set forth in

[4] FDA issued another request for nominations for the PCAC in the **Federal Register** of March 27, 2018 (83 FR 13133).

this rulemaking when evaluating bulk drug substances for inclusion on the list. FDA considers the information requested in the July 2014 Request for Nominations and bases its decision on the physical and chemical characterization, safety, effectiveness, and historical use of the bulk drug substance in compounded drug products. If nominators believe that there is additional information relevant to those four criteria that would be helpful to consideration of nominations that are still pending with FDA for evaluation, that information can be submitted for FDA's consideration via Docket No. FDA–2015–N–3534.

With respect to the concern about challenges in submitting nominations because physicians may prescribe compounded drug products tailored to the needs of individual patients, we note that physicians and prescribers, who may have unique insights on how compounded drug products are used in particular cases, may submit information for FDA's consideration via Docket No. FDA–2015–N–3534.

(Comment 30) Some comments objected to FDA's process regarding bulk drug substances that were nominated without adequate information for FDA to evaluate the substance. One commenter requested that FDA issue letters to the parties whose nominations were rejected informing them of the specific deficiencies with the nomination. The comment described this process as resource-intensive, but necessary because access to the bulk drug substance is being ''cut off.''

(Response 30) We disagree with this comment. The July 2014 Request for Nominations identifies the information that the Agency is requesting in the nominations, and nominations containing the information requested in the July 2014 Request for Nominations will be deemed adequate.

As described in the Interim Policy Guidance, Docket No. FDA–2015–N–3534 is open to receive new nominations, including renominations of substances previously nominated with inadequate supporting information, or additional information about bulk drug substances previously nominated with adequate information to allow evaluation. FDA is evaluating new information provided to the docket on a rolling basis and is periodically adding newly nominated or renominated substances to ''Category 1'' (the category for adequately supported nominations that will be evaluated for inclusion on the 503A Bulks List) when appropriate.

(Comment 31) One comment stated that clarity is needed regarding the process by which substances that have been ''considered and rejected'' by the PCAC may be renominated. The comment noted that new or additional information about the substance may become available that warrants further evaluation by FDA and the PCAC.

(Response 31) We have considered this comment and are clarifying the process for providing additional information about substances that have been considered by the PCAC. Bulk drug substances, including those that have been evaluated by FDA and presented to the PCAC and USP, remain under consideration until they are addressed in a final rule. Individuals and organizations may submit additional information relevant to the evaluation criteria about a use proposed in the original nomination(s) for a bulk drug substance to Docket No. FDA–2015–N–3534 until that substance is addressed in an NPRM. When a substance is addressed in an NPRM, individuals and organizations may submit additional information relevant to the evaluation criteria about the use(s) evaluated for that bulk drug substance as a comment to that proposed rule. As noted above, after the substance is addressed in a final rule, individuals and organizations may submit a citizen petition to FDA under 21 CFR 10.30 asking FDA to amend the list (*i.e.,* to add or delete bulk drug substances).

If an individual or organization seeks to use a bulk drug substance that has been evaluated by FDA and not recommended in FDA's review for placement on the 503A Bulks List, for a use, dosage form, or route of administration that was not previously evaluated by FDA, or where there is otherwise a substantive change between the use of the bulk drug substance sought by the individual or organization and how it was evaluated by FDA, the individual or organization may file a citizen petition under 21 CFR 10.30 requesting that FDA reconsider its evaluation of the bulk drug substance, regardless of whether that substance has been addressed in an NPRM or final rule. In responding to such citizen petitions, FDA generally intends to consider whether, for example, the petitioner provides information not previously considered or shows a significant change in circumstances supported by scientific references that alters the Agency's analysis of the four criteria.

(Comment 32) One comment stated that FDA is only sending certain nominations to the committee and appeared to be ''approving'' some nominations without consulting the PCAC.

(Response 32) We disagree with this comment, the basis of which is unclear. FDA acknowledges that it is evaluating and consulting with USP and the PCAC only on substances that were nominated with adequate support to allow the Agency's review, as described in the Interim Policy Guidance. FDA is not, however, ''approving'' the use of any bulk drug substances or proposing to include bulk drug substances on the 503A Bulks List, without consulting USP and the PCAC.

(Comment 33) One comment stated that FDA should have consulted with the PCAC before seeking nominations for the 503A Bulks List or before the Agency evaluated the first set of bulk drug substances for inclusion on the list.

(Response 33) The statute does not require that FDA seek nominations for the 503A Bulks List, or that it consult the PCAC, at any specific stage prior to undertaking rulemaking. Section 503A requires only that FDA consult with the PCAC before issuing regulations to implement subsection (b)(1)(A)(i)(III). FDA sought nominations for the 503A Bulks List and began evaluating substances for inclusion on the list before consulting with the PCAC because this enabled the Agency to prepare robust background materials for PCAC meetings and thereby obtain more meaningful PCAC and public input prior to proposing a rule describing the criteria.

8. Availability of Ingredients for Physician Use

(Comment 34) One comment objected to the rulemaking generally as infringing on the practice of medicine and overregulating physicians' choices of ingredients that can be used in compounded drug products.

(Response 34) The FD&C Act establishes the framework for regulating the drugs that physicians may prescribe. Within this framework, once a drug becomes legally available, with certain limited exceptions, FDA does not interfere with physicians' decisions to use it when they determine that in their judgment it is medically appropriate for their patients. The Agency believes that this rulemaking is consistent with this framework and does not overregulate.

(Comment 35) The comment asserted that this action amounts to poor public health policy and will stifle innovation, because drugs will not be researched or considered for new drug applications unless they show some initial promise.

(Response 35) We disagree. FDA is carrying out its statutory mandate in a manner that seeks to protect the public

from exposure to bulk drug substances that are not suitable for use in compounded drug products. We believe it protects the public health to prevent the use of drug products for which there is insufficient evidence that benefits to the patients might outweigh possible risks. To protect human subjects and the integrity of any research, it is important that drugs generally not be studied in humans outside of an investigational new drug application.

9. ''Grandfathering In'' Use of Bulk Drug Substances

(Comment 36) One comment objected to this rulemaking generally, based on FDA's lack of regulation in this arena previously. The commenter asserted that the compounding industry has developed under State law, and use of bulk drug substances in compounding should be considered ''grandfathered in.'' The comment noted that many of the bulk drug substances at issue were in use prior to 1962.

(Response 36) We disagree with this comment. Section 503A of the FD&C Act does not provide for ''grandfathering in'' the use of bulk drug substances, including those in use prior to 1962. Moreover, FDA is considering the length and extent of the historical use of the bulk drug substance in compounded drug products when determining whether to recommend the substance for inclusion on the 503A Bulks List.

10. ''Regulatory Freeze Pending Review'' Memorandum and Executive Order 13771

(Comment 37) One comment objected to this rulemaking based on the January 20, 2017, memorandum signed by Reince Priebus on behalf of President Trump entitled ''Regulatory Freeze Pending Review'' and January 30, 2017, Executive Order 13771 entitled ''Presidential Executive Order on Reducing Regulation and Controlling Regulatory Costs'' because FDA has not identified two regulations to be eliminated.

(Response 37) The requirements outlined in Executive Orders 13771 and 13777 have been considered in issuing this final rule, and this rule will be accounted for as appropriate under both executive orders.

11. Rulemaking

(Comment 38) Some commenters alleged that FDA's actions related to this rulemaking, many of which are described in the comments summarized above, have been arbitrary and capricious in violation of the Administrative Procedure Act (APA) (5 U.S.C. 551 *et seq.*). In addition, one commenter stated that FDA's actions through this rulemaking are arbitrary and capricious because the rulemaking goes beyond concerns about the safety of compounded drug products, which applies only to sterile drug products. That commenter noted that Congress enacted the DQSA to address concerns surrounding sterility and contamination.

(Response 38) We disagree with this comment. FDA has followed proper rulemaking procedures and has not acted in an arbitrary and capricious manner in violation of the APA.

Section 503A requires FDA to issue the 503A Bulks List through a rulemaking process, and it gives the Agency discretion to consider relevant criteria (see section 503A(c)(2) of the FD&C Act). FDA is establishing the four criteria described above, and applying these criteria to bulk drug substances that are not the subject of an applicable USP–NF monograph or a component of an FDA-approved drug product. Such substances may be used to compound sterile or non-sterile drug products. Accordingly, FDA applies the established criteria to bulk drug substances that may be used to compound sterile or non-sterile drug products. FDA notes that the safety criterion is not limited to consideration of sterility and contamination, and FDA may have safety concerns about bulk drug substances used to compound sterile and non-sterile drug products.

VI. Effective Date

This final rule will become effective 30 calendar days after the date of its publication in the **Federal Register**.

VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.'' We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we do not have enough information about the effect of the final rule on small entities, we find that the final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

We evaluated 10 bulk drug substances for this final rule. We will place six bulk drug substances on the 503A Bulks List, and we will not place four substances on the 503A Bulks List. We expect that the rule will affect compounding pharmacies and other producers that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected substances, and payers that cover these drug products or alternative treatments. Because we lack sufficient information to quantify most of the costs and benefits of this final rule, we also include a qualitative description of potential benefits and potential costs.

In table 1, we summarize the impacts of the final rule. The present value of the costs of the final rule equals $3.33 million at a 7 percent discount rate and $3 million at a 3 percent discount rate. The final rule will result in annualized costs of $0.42 million at a 7 percent discount rate, or $0.31 million at a 3 percent discount rate.

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE FINAL RULE

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered (years)	
Benefits:							
Annualized Monetized ($m/year)	.....	.....	.....	.....	.....	.....	
Annualized Quantified	.....	.....	.....	.....	.....	.....	
Qualitative	Potential gains or losses in consumer surplus, depending on consumer preferences for compounded drugs. Potential public health benefits from increased use of other drug products that may be more effective.						
Costs:							
Annualized Monetized ($m/year)	$0.42	$0.27	$0.56	2016	7	10	
Annualized Quantified	0.31	0.21	0.42	2016	3	10	
Qualitative	Costs to submit INDs for some compounded drug products.						
Transfers:							
Federal Annualized Monetized ($m/year)	From:			To:			
Other Annualized Monetized ($m/year)	From:			To:			
Effects: State, Local, or Tribal Government: None. Small Business: None. Wages: None. Growth: None.							

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 17) and at *https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, FDA is not required to seek clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov*. References without asterisks have copyright restriction and can be viewed at Dockets Management Staff. They are not available publicly on the internet due to copyright restriction. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

* 1. Food and Drug Administration, FDA Guidance for Industry on Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, 2017; available at *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf*.

* 2. Food and Drug Administration, Transcript of the February 23, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015; available at *https://wayback.archive-it.org/7993/20170404155240/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf*.

* 3. Memorandum to File on Food and Drug Administration Consultations with United States Pharmacopeia, September 26, 2016.

* 4. Letter from the United States Pharmacopeia to FDA, October 7, 2016.

* 5. Food and Drug Administration Briefing Document for the June 17–18, 2015,

Meeting of the Pharmacy Compounding Advisory Committee, 2015; available at *https://wayback.archive-it.org/7993/20170405230419/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf.*

6. Birdsall, T.C., 1998, ''5-Hydroxytryptophan: A Clinically-Effective Serotonin Precursor,'' *Alternative Medicine Review,* 3(4):271–80; available at *https://www.ncbi.nlm.nih.gov/pubmed/9727088.*

7. MedlinePlus, 5–HTP; available at *https://medlineplus.gov/druginfo/natural/794.html* (last reviewed November 30, 2017).

* 8. Drugs.com, Prozac Side Effects, 2018; available at *https://www.drugs.com/sfx/prozac-side-effects.html.*

9. Jakoben, J.C., K.K. Katakam, A. Schou, et al., 2017, ''Selective Serotonin Reuptake Inhibitors Versus Placebo in Patients with Major Depressive Disorder. A Systematic Review with Meta-Analysis and Trial Sequential Analysis.'' *BMC Psychiatry,* 17(1):58.

* 10. Food and Drug Administration Supplemental Review of Oxitriptan, November 2018.

11. Fang, Y., Z. Qiu, W. Hu, et al., 2014. ''Effect of Piracetam on the Cognitive Performance of Patients Undergoing Coronary Bypass Surgery: A Meta-Analysis.'' *Experimental and Therapeutic Medicine,* 7:429–434; available at *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3881046/.*

12. De Reuck, J. and B. Van Vleymen, 1999, ''The Clinical Safety of High-Dose Piracetam—Its Use in the Treatment of Acute Stroke.'' *Pharmacopsychiatry,* 32 Suppl 1:33–37; available at *https://www.ncbi.nlm.nih.gov/pubmed/10338106.*

* 13. Food and Drug Administration Briefing Document for the February 23–24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015; available at *https://wayback.archive-it.org/7993/20170405230436/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf.*

14. UCB Pharma SA, 2007. A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 9600 and 4800 mg/day piracetam (oral 800 mg tablets, b.i.d.) taken for 12 months by subjects suffering from mild cognitive impairment (MCI) Brussels: UCB, Inc. Clinical Study Summary; available at *https://www.ucb.com/_up/ucb_com_patients/documents/N01001_CSS_20070907.pdf.*

* 15. Food and Drug Administration, Transcript of the February 24, 2015, Meeting of the Pharmacy Compounding Advisory Committee; available at *https://wayback.archive-it.org/7993/20170404155242/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf.*

* 16. Food and Drug Administration Supplemental Review of Topical Tranilast, April 25, 2016.

* 17. Economic Analysis of Impacts, available at *https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is amended as follows:

PART 216—HUMAN DRUG COMPOUNDING

■ 1. The authority citation for part 216 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.

■ 2. Add § 216.23 to subpart B to read as follows:

§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

(a) The following bulk drug substances can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

(1) Brilliant Blue G, also known as Coomassie Brilliant Blue G–250.

(2) Cantharidin (for topical use only).

(3) Diphenylcyclopropenone (for topical use only).

(4) N-acetyl-D-glucosamine (for topical use only).

(5) Squaric acid dibutyl ester (for topical use only).

(6) Thymol iodide (for topical use only).

(b) After balancing the criteria set forth in paragraph (c) of this section, FDA has determined that the following bulk drug substances will not be included on the list of substances that can be used in compounding set forth in paragraph (a) of this section:

(1) Oxitriptan.

(2) Piracetam.

(3) Silver Protein Mild.

(4) Tranilast.

(c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:

(1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;

(3) The available evidence of the effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and

(4) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Dated: February 11, 2019.

Scott Gottlieb,

Commissioner of Food and Drugs.

[FR Doc. 2019–02367 Filed 2–15–19; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF DEFENSE

Office of the Secretary of Defense

32 CFR Part 162

[Docket ID: DOD–2018–OS–0084]

RIN 0790–AK46

Productivity Enhancing Capital Investment (PECI)

AGENCY: Under Secretary of Defense (Personnel and Readiness), DoD.

ACTION: Final rule.

SUMMARY: This final rule removes the DoD regulation issued to explain to contractors how the Productivity Enhancing Capital Investment (PECI) program could be used by DoD components to fund projects that improve productivity. This rule implemented an Executive Order which has since been revoked. The associated internal programs were discontinued, and internal guidance was cancelled. The content of this part is obsolete.

DATES: *Effective Date:* This rule is effective on February 19, 2019.

FOR FURTHER INFORMATION CONTACT: Dana F. Kline, 703–695–4506, *dana.f.kline.civ@mail.mil.*

SUPPLEMENTARY INFORMATION: It has been determined that publication of this CFR part removal for public comment is

APPENDIX 4: Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency (July 2019)

Contains Nonbinding Recommendations

Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency

Immediately in Effect Guidance for Industry

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Tracy Rupp (CDER) at tracy.rupp@fda.hhs.gov.

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2019
Compounding

Table of Contents

Compliance Policy for Certain Compounding of Oral Oxitriptan (5-HTP) Drug Products for Patients With Tetrahydrobiopterin (BH4) Deficiency
Immediately in Effect Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA, the Agency, or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA, we, or the Agency) policy concerning the conditions under which the Agency does not generally intend to take regulatory action against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician using the bulk drug substance oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) to compound oral drug products for patients with tetrahydrobiopterin (BH4) deficiency.[2,3] On February 19, 2019, FDA issued a final rule (84 FR 4696) ("final rule") that established the list of bulk drug substances that can be used to compound drug products under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), even though they are not the subject of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph or a component of an FDA approved drug product (503A Bulks List).[4] The final rule, codified at 21 CFR 216.23, placed six bulk drug substances on the 503A Bulks List (21 CFR 216.23(a)), and identified four others, including oxitriptan, that cannot be used to compound drug products under section 503A of the FD&C Act (21 CFR 216.23(b)). Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future rulemaking.

FDA developed this guidance in response to communications from pharmacists and caregivers regarding the use of oxitriptan to treat patients with BH4 deficiency following issuance of the final rule. According to those communications and other information available to the Agency,

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Tetrahydrobiopterin (BH4) deficiency is also known as: primary tetrahydrobiopterin deficiency, atypical phenylketonuria (PKU), GTP cyclohydrolase (GTPCH) deficiency, 6-pyruvoyl-tetrahydropterin synthase (6-PTPS) deficiency, and dihydropteridine reductase (DHPR) deficiency.

[3] This guidance does not apply to drugs compounded for use in animals.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] See section 503A(b)(1)(A) of the FD&C Act [21 U.S.C. 353a(b)(1)(A)].

oxitriptan is the standard of care for the treatment of BH4 deficiency, which is caused by several different rare enzyme defects that result from gene mutations. Thus, this guidance addresses the conditions under which FDA does not intend to take regulatory action against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician for the use of bulk oxitriptan to compound oral drug products for the treatment of identified individual patients with BH4 deficiency.

We are issuing this guidance consistent with our good guidance practices (GGP) regulation (21 CFR 10.115). This guidance is immediately effective because FDA has determined that prior public participation is not feasible or appropriate due to the public health need for patients with BH4 deficiency to access compounded oxitriptan oral drug products (21 CFR 10.115(g)(2)).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Compounding From Bulk Drug Substances Under Section 503A of the FD&C Act

Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from certain requirements of the FD&C Act related to FDA approval prior to marketing, current good manufacturing practice requirements, and labeling with adequate directions for use (sections 505, 501(a)(2)(B), and 502(f)(1)) [21 U.S.C. 355, 351(a)(2)(B), and 352(f)(1)].

One of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by FDA; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by FDA, appear on a list of bulk drug substances developed by FDA through regulation.[5]

B. History of Rulemaking Involving Oxitriptan Under Section 503A of the FD&C Act

Because oxitriptan is neither the subject of an applicable USP or NF monograph nor a component of an FDA-approved drug, use of bulk oxitriptan to compound a drug product under section 503A

[5] See section 503A(b)(1)(A)(i) of the FD&C Act [21 U.S.C. 353a(b)(1)(A)(i)].

of the FD&C Act requires that oxitriptan be placed on the 503A Bulks List.[6] Oxitriptan was nominated and evaluated for inclusion on the 503A Bulks List for use in the treatment of insomnia and depression, not BH4 deficiency. FDA convened an advisory committee to seek its advice about whether to include a number of bulk drug substances, including oxitriptan, on the 503A Bulks List.[7] Based on its review and applying the criteria identified in the Federal Register (79 FR 37747), FDA proposed to the Pharmacy Compounding Advisory Committee (PCAC) that oxitriptan not be included on the 503A Bulks List.[8] At the PCAC meeting on June 17, 2015, the committee voted to recommend to FDA not to include oxitriptan on the 503A Bulks List.[9] Taking into consideration the PCAC's advice, and after consultation with USP, FDA determined that, on balance, the criteria that it considers when conducting evaluations for the 503A Bulks List weighed against inclusion of oxitriptan on the 503A Bulks List.

On December 16, 2016, FDA published a proposed rule (81 FR 91071) to not include oxitriptan on the 503A Bulks List and provided for a 90-day period to allow for comments to be submitted for FDA's consideration in finalizing the rule. In the preamble to the December 16, 2016 proposed rule, FDA stated that, on balance, the criteria weighed against the inclusion of oxitriptan on the 503A Bulks List. In particular, the Agency's evaluation of oxitriptan revealed serious safety concerns related to the use of oxitriptan for depression, a potentially life-threatening condition, in lieu of, or causing a delay in, treatment with an available approved product and the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking a compounded oxitriptan drug product. Such risks include, for example, the concomitant use of oxitriptan with antidepressant drugs, which could result in serotonin syndrome, a serious and life-threatening drug interaction (81 FR 91078).

The Agency received comments to the 2016 proposed rule, some of which related to oxitriptan. None of the comments identified treatment of BH4 deficiency as a proposed use of compounded oxitriptan drug products. On February 19, 2019, FDA issued a final rule in the *Federal Register* that identified four bulk drug substances, including oxitriptan, that FDA considered and did not include on the 503A Bulks List (84 FR 4696). The rule became effective on March 21, 2019.

Following publication of the February 19, 2019 final rule, several pharmacists and caregivers contacted FDA to advise the Agency that oxitriptan is an essential and standard treatment for patients with BH4 deficiency, a rare genetic disorder characterized by deficiency of the cofactor BH4 which leads to deficiency of the neurotransmitter serotonin (and its precursor 5-hydroxy-tryptophan) within the central nervous system. As noted above, FDA did not consider BH4 deficiency during its initial review of this substance for the 503A Bulks List.

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[6] See section 503A(c)(2) of the FD&C Act [21 U.S.C. 353a(c)(2)].
[7] See section 503A(c)(1) of the FD&C Act [21 U.S.C. 353a(c)(1)].
[8] See https://wayback.archive-it.org/7993/20170405230419/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf.
[9] See https://wayback.archive-it.org/7993/20170404155231/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf.

III. POLICY

In light of the information brought to the Agency's attention about the standard of care for treating patients with BH4 deficiency, FDA does not intend to take action for violations of sections 501(a)(2)(B), 502(f)(1), or 505 of the FD&C Act against a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician who compounds with the bulk drug substance oxitriptan, provided the following conditions are met:

- The compounded oxitriptan-containing drug product is intended only for oral administration;
- The compounder provides the oxitriptan-containing oral drug product solely for identified individual patients with BH4 deficiency, after receiving a valid prescription for such identified individual patient indicating the diagnosis;[10]
- The compounder maintains records documenting that the drug product was compounded for a patient with BH4 deficiency; and
- All other conditions of section 503A and other applicable requirements of the FD&C Act and FDA regulations are met.

FDA intends to take regulatory action against entities that compound drug products using bulk oxitriptan for non-oral routes of administration or to treat conditions other than BH4 deficiency. FDA intends to evaluate compliance during inspections by reviewing information (e.g., documentation on prescriptions) stating whether the drug product was compounded for an identified individual patient with BH4 deficiency.

In light of the new information regarding use of oral oxitriptan to treat BH4 deficiency, FDA is considering whether to reevaluate the exclusion of oxitriptan from the 503A Bulks List.

[10] If the prescription does not specify that the identified patient has been diagnosed with BH4 deficiency, the compounder should contact the prescriber to obtain and document this information.

Tab 5

Neomycin Sulfate

Tab 5a

FDA Evaluation of Neomycin Sulfate

DATE: May 7, 2021

FROM: Alma Davidson, M.D.
Medical Officer, Division of Anti-Infectives (DAI), Office of Infectious Diseases (OID), CDER

Peter Kim, M.D., M.S.
Clinical Team Leader, DAI, OID, CDER

Hala Shamsuddin, M.D.
original reviewer from DAI

Joseph Toerner, M.D., MPH
Director, Division of Hepatology and Nutrition (DHN)

THROUGH: Sumathi Nambiar, M.D., M.P.H.
Director, DAI, OID, CDER

John Farley, M.D., M.P.H.
Director, OID, CDER

Joyce Korvick, M.D., MPH
Deputy Director for Safety, Division of Gastroenterology (DG), Office of Immunology and Inflammation (OII), CDER

Julie Beitz, M.D.
Office Director, Office of Immunology and Inflammation (OII) CDER

Frances Gail Bormel, R.Ph, J.D.
Office Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Parenteral Neomycin Sulfate for the Withdrawn or Removed List

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from three sections of the FD&C Act.[1] One of the conditions that must be satisfied to qualify for the exemptions under section 503A is that the licensed pharmacist or licensed physician "does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective."[2]

Section 503B of the FD&C Act describes the conditions that must be satisfied for a drug compounded for human use by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility to be exempt from three sections of the FD&C Act.[3] One of the conditions in section 503B of the FD&C Act that must be satisfied to qualify for the exemptions is that "[t]he drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective."[4]

FDA has established a list of drug products that were withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective, and which may not be compounded under the exemptions provided by section 503A(a) or section 503B(a) of the FD&C Act (the Withdrawn or Removed List).[5]

The Office of Compounding Quality and Compliance (OCQC) asked the Division of Anti-Infectives (DAI) and the Division of Hepatology and Nutrition (DHN) to provide input on whether parenteral neomycin sulfate should be included on the Withdrawn or Removed List.

II. DIVISION OF ANTI-INFECTIVES, OFFICE OF INFECTIOUS DISEASES, CDER

Evaluation of Parenteral Neomycin Sulfate for the Withdrawn or Removed List

The Office of Compounding Quality and Compliance (OCQC) asked the Division of Anti-Infectives (DAI) to provide input on three questions related to whether parenteral neomycin sulfate should be included on the Withdrawn or Removed List and, if yes, on how the drug should be described on the list. The three questions and DAI's responses are provided here.

[1] FD&C Act sections 505 (concerning the approval of new drugs under new drug applications (NDAs) or abbreviated new drug applications), 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and 501(a)(2)(B) of the (concerning current good manufacturing practice).
[2] See section 503A(b)(1)(C).
[3] FD&C Act sections 502(f)(1), 505, and 582 (concerning drug supply chain security).
[4] See section 503B(a)(4).
[5] See 21 CFR 216.24.

***Question 1*:** Based on the information available, do you agree that parenteral neomycin sulfate drug products were withdrawn or removed from the market for safety reasons? Please summarize the basis for the withdrawal or removal of the drug from the market citing available evidence where appropriate.

DAI Response:

Summary of Information on Neomycin Sulfate

Neomycin sulfate is an aminoglycoside antibacterial drug that was discovered in 1949. Prior to 1970, approved labeling of certain drug products containing neomycin sulfate indicated the drug as an intramuscular (IM) injection in certain serious systemic infections and urinary tract infections (UTIs), for intraperitoneal instillation in the treatment of peritonitis and in the prevention of peritonitis after intraabdominal spillage, for intestinal instillation in emergency abdominal surgery, and for topical use as wet dressings, packs and irrigations (44 FR 44180). The pre-1970 precautions section of the approved labeling for these drug products warned of the drug's potential to cause ototoxicity and nephrotoxicity (44 FR 44180). The approved labeling from this time for other drug products containing neomycin sulfate, specifically nonsterile neomycin sulfate for prescription compounding, contained no warnings about the risks associated with these products (see Appendix 4).

As a result of the Drug Efficacy Study Implementation (DESI), FDA published a *Federal Register* notice on May 13, 1970 (35 FR 7464) stating that the Agency "conclude[d] that when administered intramuscularly neomycin sulfate powder is probably effective for the indications described in the labeling guidelines in this announcement." The notice requested that holders of approved applications for neomycin sulfate sterile powder submit amendments to their applications to revise the labeling to provide the following information concerning its indications: "Intramuscular use of neomycin sulfate should be restricted to hospitalized patients with severe systemic infections, due to the following organisms, when these are resistant to other less toxic antimicrobials but susceptible to neomycin: [*P. aeruginosa*, *K. pneumoniae*, *P. vulgaris*, *E. coli*, *E. aerogenes*, and *H. influenzae*]. Neomycin sulfate has been successfully used in urinary tract infections due to susceptible pathogens, but should be reserved for cases in which no other antimicrobial agent is effective" (see Appendix 1). The *Federal Register* notice provided for opportunity to comment or submit pertinent data supporting the indications.

The 1970 *Federal Register* notice's announcement was amended by a *Federal Register* notice published on February 29, 1972 (37 FR 4224). The 1972 notice stated that, with respect to neomycin sulfate sterile powder, "[t]he effectiveness classification of the following indications is changed from probably effective to effective: For intramuscular use in the treatment of urinary tract infections due to susceptible strains of the following organisms: [*P. aeruginosa*, *K. pneumoniae*, *P. vulgaris*, *E. coli*, and *E. aerogenes*]." The 1972 notice amended the indications set forth in the labeling guidelines that were originally announced in the 1970 notice to state as follows: "Neomycin sulfate may be indicated in treatment of urinary tract infections due to susceptible strains: [*P. aeruginosa*, *K. pneumoniae*, *P. vulgaris*, *E. coli*, and *E. aerogenes*]. Because of its potential toxicity it should be reserved for hospitalized cases in which no other antimicrobial agent is effective." The labeling guideline was also amended to include a Boxed Warning regarding nephrotoxicity, ototoxicity, and respiratory paralysis due to

neuromuscular blockade. Further, the 1972 notice stated that "[t]he remaining probably effective indication and the possibly effective indications have been reclassified as lacking substantial evidence of effectiveness in that no new evidence of effectiveness of this drug has been submitted pursuant to the notice of May 13, 1970. No effective indications remain for other than the intramuscular route of administration." Additionally, the *Federal Register* notice stated that "[p]ackagescontaining 5 or 10 grams of sterile powder are considered inappropriate sizes for preparation of solutions for intramuscular administration and will no longer be certified or released" (see Appendix 2). In a *Federal Register* notice published on February 29, 1972 (37 FR 4188), FDA concluded that the antibiotic drug regulations should be amended to reflect the conclusions in the notice published at 37 FR 4224. Accordingly, the regulation at 21 CFR § 148i.1 was amended to provide that "each immediate container shall contain 0.35 gram of neomycin" (see Appendix 3).

On April 4, 1977, the Anti-Infective Advisory Committee (the Committee) discussed neomycin sulfate in sterile vials for parenteral use. The summary minutes of the meeting state as follows with respect to these products:

> This is a currently marketed dosage form of neomycin although, after the DESI publications on this drug, only one indication remains. This if [sic] for use in urinary tract infections where other antibiotics are not effective. It is apparant [sic] that some portion of the drug that is certified is used for irrigation although there is no labeling indication for such a use. In fact the DESI announcement has downgraded this dosage form for this indication as showing no substantial evidence of effectiveness. The Committee was quite concerned about possible unlabeled use fearing possible toxicity. Since they believed that there is essentially no use of the dosage form for the labeled indication, the Committee concluded that the risk/benefit judgement did not warrant continued marketing. They unanimously recommended that the dosage form no longer be certified. They believed that considering the potential toxicity, other drugs with less toxicity are available for the single labeled use.

Additionally, the Committee discussed non-sterile neomycin bulk for prescription compounding. The summary minutes of the meeting state as follows with respect to these products:

> This form of neomycin is supplied in bulk form in non-sterile 100 mg vials. There is no labeling for this dosage form. It is used by hospital pharmacies and others to formulate a number of other dosage forms.
>
> One firm supplying this drug has suggested to FDA that it be accompanied by a warning label. Neither the types of dosage forms nor concentration can be controlled and toxic effects have occurred from its use. Some compounders wishing to formulate neomycin have used the parenteral vial discussed above to avoid the necessity of sterilization before use as an irrigant.
>
> Some members felt that the risk associated with the uses of the bulk as an irrigant would be reduced if instructions were given to reduce the level of neomycin.

Since effectiveness studies are not available for any concentration of neomycin, this alternative was not recommended.

The Committee concluded that a warning label should be placed on this neomycin product immediately. Committee members will frame black box warning. Firms manufacturing the product will be notified to add the warning and will be on notice that since there is no evidence of effectiveness for the common uses, data will be required (see Appendix 4 – Summary Minutes).

In a notice published in the *Federal Register* of July 27, 1979 (44 FR 44180), FDA proposed to amend the antibiotic regulations to revoke provisions for certification of neomycin sulfate in sterile vials for parenteral use (see Appendix 5), based on the findings of the Anti-Infective Advisory Committee and the widespread evidence that the drug's risks outweighed its benefits. The notice stated that there was clinical evidence that "significant amounts of neomycin sulfate are systemically absorbed following dosing by most routes of administration", and that neomycin sulfate has induced significant toxicity by the various parenteral routes (IM, intra-pleural, intra-peritoneal, etc.), and described how this systemic exposure may result in serious nephrotoxicity, ototoxicity, and neuromuscular paralysis with respiratory arrest. The notice stated that "[o]totoxicity is progressive to involve the entire auditory frequency range. It can occur abruptly or insidiously, at doses as low as 2 g, and may progress days, weeks, and even months after discontinuation of the drug …. [O]totoxicity caused by neomycin sulfate is irreversible." The notice also described how neomycin sulfate exposure may also result in cross-sensitization to structurally related aminoglycosides. The notice stated that FDA was particularly concerned about the risk of cross-sensitization because it may preclude future therapy with other potentially lifesaving aminoglycoside antibiotics, and noted that FDA had received a number of adverse reaction reports telling of hypersensitivity reaction to neomycin sulfate. The notice specifically mentioned concerns regarding wound irrigation, stating that such use has been found to be without substantial evidence of effectiveness. The notice stated that there is no evidence to provide safe concentrations and safe dosage limits for this use, there was evidence that significant amounts of neomycin sulfate are absorbed systemically following its use in an irrigant solution during surgery, amounts that are comparable to amounts absorbed from an intramuscular injection site. The notice stated that use of neomycin sulfate as an irrigant may thus cause the same toxic effects as are produced by intramuscular administration, and that the Agency had received reports of total or partial deafness, kidney failure, heart arrest, paralysis, and coma with respect to this use.

In a notice published in the *Federal Register* of July 27, 1979 (44 FR 44178), FDA proposed to amend the antibiotic drug regulations by revoking provisions for certification of nonsterile neomycin sulfate for prescription compounding. In the preamble to the proposed rule, FDA explained that "the drug is being used for indications for which it lacks evidence of effectiveness and for which there is clinical evidence of significant risk to the patient." Specifically, FDA pointed to "information that . . . nonsterile neomycin sulfate for prescription compounding is being sterilized or otherwise processed for use in irrigation solutions and for other uses in the treatment of conditions for which the drug lacks evidence of effectiveness." The Agency considered evidence that "strongly suggests that the drug is being used to prepare solutions that are then sterilized and used for intraperitoneal irrigations, intrapleural irrigations, and irrigations

of other surgical wounds." According to FDA, "there is evidence that significant amounts of the drug are absorbed systemically following its use in irrigation solution, amount comparable to amounts absorbed when the drug is taken systemically." This in turn, FDA explained, could result in the same serious toxic effects as systemic use. Thus, FDA stated that "[b]ecause sufficient data to ensure adequately the safe and effective use of neomycin sulfate for prescription compounding currently do not exist, the agency does not believe that the continued marketing of the drug pending the submission of further data . . . is justified" (see Appendix 6).

Subsequently, in 1988 FDA published a series of notices about neomycin sulfate in the *Federal Register* under three separate docket numbers— FDA-1979-N-0256, FDA-1979-N-0220, and FDA-1987-D-0240.[6]

FDA published a final rule on April 15, 1988 (53 FR 12658) under docket number FDA-1979-N-0256 amending the antibiotic drug regulations to revoke the provisions for certification of neomycin sulfate in sterile vials for parenteral use (see Appendix 7). As a result of the final rule, neomycin sulfate packaged in sterile vials for dispensing could no longer be certified or released. As the notice explained, this action was taken because the risks involved in the parenteral use of neomycin sulfate were judged to outweigh any benefits that might have been derived from its continued availability. FDA offered an opportunity for a hearing on objections to the revocation.

FDA also published a second notice on April 15, 1988 (53 FR 12664) under docket number FDA-1979-N-0256 proposing to withdraw approval of four abbreviated antibiotic drug applications (AADAs) for neomycin sulfate in sterile vials for parenteral use. Consistent with the final rule revoking the antibiotic regulation for certification of neomycin sulfate in sterile vials for parenteral use (53 FR 12658), this notice stated FDA's finding that neomycin sulfate in sterile vials is unsafe for parenteral use as provided for in its approved labeling. In addition to revising the applicable regulations described above for neomycin sulfate in sterile vials for parenteral use, the withdrawal of these applications was necessary to remove the existing approved products from the market. FDA provided an opportunity for a hearing on these proposed withdrawals (see Appendix 8).

In a subsequent notice published in the *Federal Register* of December 6, 1988 (53 FR 49232) under docket number FDA-1979-N-0256, FDA withdrew approval of the same four AADAs for neomycin sulfate in sterile vials for injection for which the holders had waived their opportunity for a hearing (see Appendix 9).

In another notice of the *Federal Register* of April 15, 1988 (53 FR 12644), FDA published a final rule under docket number FDA-1979-N-0220 amending the antibiotic drug regulations pertaining to the certification of nonsterile neomycin sulfate for prescription compounding. Based on its evaluation of the written and oral comments received on the 1979 proposed rule (44 FR 44178), and based on other information, the Agency did not revoke the provisions for certification of non-sterile neomycin sulfate for prescription compounding but instead revised

[6] These dockets were originally assigned docket numbers 79N-0151, 79N-0155, and 87D-0315. The numbers were changed to FDA-1979-N-0256, FDA-1979-N-0220, and FDA-1987-D-0240, respectively, as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

them. In the preamble to the final rule, FDA found that "the risks of adverse reactions from the use of neomycin sulfate irrigations are significantly greater than any demonstrated benefits. Safety and efficacy have been demonstrated for a number of less toxic alternatives to the local instillation of neomycin sulfate in surgical procedures." However, FDA also found that "[t]he risk versus benefit considerations are different for orally administered neomycin sulfate. Because systemic absorption is low with oral administration, the risk of toxicity is reduced." Furthermore, the Agency found that "[a]dequate evidence supports the effectiveness of neomycin sulfate oral tablet and oral solution preparations as adjuctive therapy for preoperative suppression of intestinal bacteria and for treatment of hepatic coma." Thus, the Agency concluded that the benefits of orally administered neomycin sulfate outweighed the risks for these two indications. Accordingly, the final rule revised the antibiotic drug regulations by changing the product name from "neomycin sulfate for prescription compounding" to "neomycin sulfate for compounding oral products" and to require labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use (see Appendix 10).

FDA also announced under docket number FDA-1987-D-0240 in the same issue of the *Federal Register* (53 FR 12662), the availability of guideline labeling for neomycin sulfate for compounding oral products (formerly neomycin sulfate for prescription compounding) and a proposal to withdraw approval of six antibiotic drug applications (ADAs) and AADAs for nonsterile neomycin sulfate products unless the application holders submitted supplemental applications providing for a product name and labeling consistent with the revised name and labeling requirements described in the newly-amended antibiotic drug regulations (see 53 FR 12644) (see Appendix 11). As the notice explained, FDA proposed the withdrawal of approval of the six applications because nonsterile neomycin sulfate, a prescription drug with a recognized potential for producing toxicity, was being supplied for prescription compounding without adequate labeling and the drug was being used for indications for which it lacked evidence of effectiveness and for which there was clinical evidence of significant risk to the patient. Accordingly, the notice stated that on the basis of the data and information that was available to the Agency, FDA concluded that nonsterile neomycin sulfate was unsafe for use except when named "Neomycin Sulfate for Compounding Oral Products" and used in accordance with appropriate package insert labeling. In addition to revising the applicable regulations described above pertaining to the certification of non-sterile neomycin for prescription compounding, the proposed withdrawal of these applications was necessary to accomplish the desired action. FDA provided an opportunity for a hearing on the proposal to withdraw approval of the six applications.

On December 6, 1988, FDA published a notice in the *Federal Register* (53 FR 49231) announcing the withdrawal of approval of five of the six applications for neomycin sulfate for prescription compounding described in the notice from 53 FR 12662 summarized above for which the holders had waived their opportunity for a hearing and did not supplement their applications (see Appendix 12). However, the AADA for nonsterile neomycin sulfate for prescription compounding, AADA 61-579, held by Pharma-Tek, Inc. (Pharm-Tek), PO Box AB, Huntington NY 11743, was not withdrawn at that time because a hearing had been requested by Pharma-Tek and was under consideration by the Agency. This application corresponded to

abbreviated new drug application (ANDA) 61-579, which had most recently been held by X-Gen Pharmaceuticals, Inc (X-Gen).[7]

Hearing requests dated May 13, 1988 were submitted on behalf of Pharma-Tek, regarding the matters under all four notices about neomycin sulfate published on April 15, 1988. Additional materials in support of these hearing requests as well as in support of a petition for stay of action on these matters were filed on behalf of Pharma-Tek on August 12, 1988 and December 30, 1988. The hearing did not take place, however.

In the *Federal Register* of October 8, 1998 (63 FR 54082), FDA included "all parenteral drug products containing neomycin sulfate" in its proposed rule to establish the Withdrawn or Removed List (the 1998 proposed rule) based on the findings and regulatory actions described previously (see Appendix 13).

In the final rule for the "List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness," which was published in the *Federal Register* of March 8, 1999 (64 FR 10944), FDA addressed a comment received on the 1998 proposed rule regarding the proposal to include all parenteral drug products containing neomycin sulfate on the Withdrawn or Removed List (see Appendix 14). The comment pointed out that there was a hearing request pending before the Agency regarding the withdrawal of approval of the applications for neomycin sulfate in sterile vials for injection (53 FR 49232) and another pending request for a hearing regarding the withdrawal of approval of the applications for neomycin sulfate for prescription compounding (53 FR 49231). FDA also observed in the preamble to the final rule that a petition for stay of action regarding the two actions mentioned above and regarding a labeling guideline for neomycin sulfate for prescription compounding (53 FR 12662) was also pending with the Agency. FDA then noted in the preamble to the 1999 final rule for the Withdrawn or Removed List that because of the complex administrative record on neomycin sulfate then before the Agency and because of the public health need to expedite implementation of this rule, FDA was postponing final action on listing all parenteral drug products containing neomycin sulfate. FDA stated that parenteral drug products containing neomycin sulfate may be added to the list at a later date.

On August 6, 2012, FDA filed a memorandum with the Division of Dockets Management regarding Pharma-Tek's challenges to the proposed withdrawal of approval of AADA 61-579/ANDA 061579 and to the regulatory actions underlying it. The memorandum states that Pharma-Tek filed a total of four citizen petitions requesting a stay of action, three dated August 12, 1988, and one dated December 30, 1988. The memorandum states that the Agency sent a letter via certified mail to X-Gen (Pharma-Tek's successor with respect to AADA 61-579/ANDA 061579) on June 18, 2012 requesting that it affirmatively inform the Agency if it

[7] The terms antibiotic drug applications (ADAs) and abbreviated antibiotic drug applications (AADAs) are no longer used. As explained in the "Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act," section 125 of the Food and Drug Administration Modernization Act of 1997 provided that all full applications approved under section 507 on or before November 20, 1997, were deemed to have been submitted and filed under section 505(b) and approved for safety and effectiveness under section 505(c), and that all abbreviated applications approved under section 507 of the FD&C Act on or before November 20, 1997, were deemed to have been filed and approved under section 505(j) of the FD&C Act.

wanted the petitions to remain active. The letter stated that if the Agency did not receive a written response within 30 days from the date of the letter, the petitions would be considered to have been voluntarily withdrawn without prejudice to resubmission. The memorandum states that, because the Agency did not receive a response within the allotted time, the four citizen petitions (among them, the one identified in the preamble of the 1999 final rule) requesting a stay of action regarding withdrawal of approval of applications for neomycin sulfate products had been voluntarily withdrawn without prejudice (see Appendix 15).

On October 9, 2015, X-Gen issued a letter informing FDA that it was withdrawing the hearing request previously filed on behalf of its predecessor Pharma-Tek concerning docket number FDA-1987-D-0240, as well as hearing requests filed on behalf of Pharma-Tek concerning docket numbers FDA-1979-N-0256 and FDA-1979-N-0220, including in relation to ANDA 061579. X-Gen also informed FDA that it waived the opportunity for a hearing and, under 21 CFR 314.150(d), X-Gen permitted the Agency to withdraw approval of ANDA 061579 for neomycin sulfate for prescription compounding (see Appendix 16).

In a notice published in the *Federal Register* of February 5, 2019 (84 FR 1746), FDA announced the withdrawal of approval of ANDA 061579 for nonsterile neomycin sulfate powder for prescription compounding. As the notice explained, the basis for the withdrawal is that the product is no longer considered safe as labeled due to clinical evidence that systemic exposure to neomycin sulfate can induce significant toxicity including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade. The holder of this ANDA had waived its opportunity for a hearing (see Appendix 17).

DAI's Assessment

The medical dictionary[8] defines "parenteral" as "by some route other than through the alimentary canal" and is generally understood to mean administration other than by the oral route and particularly to contemplate administration by injection, infusion, or implantation.[9] We note that dermatologic products administered topically are not considered to be administered parenterally. As summarized in the preceding section, DESI assessments, assessments by the Anti-Infective Advisory Committee, and other assessments described in FDA's notices concerning neomycin sulfate have referred to multiple forms of parenteral uses, including IM uses and instillation in, or irrigation of, body spaces and structures. The final rule published in the *Federal Register* of April 15, 1988 (53 FR 12644) addressed the following uses of nonsterile neomycin sulfate for prescription compounding: in the treatment of infected wounds and ulcers; for use in burns; for prophylactic local use before, during, or after surgical procedures (e.g., intraperitoneal suction-irrigation, fractures, joint replacement surgery, neurosurgery and for other types of surgery, and traumatic wounds); for rectal or colonic irrigation or as a retention enema; for intrapleural instillations; for use in wet dressings; for aerosol inhalation; for solutions to soak bone grafts, skin grafts, silastic implants, and for any similar use under conditions where neomycin sulfate may be systemically absorbed in significant quantities. The FDA determined that the risk/benefit analysis for all these uses was not favorable.

[8] See http://medical-dictionary.thefreedictionary.com/parenteral.

[9] See Route of Administration, U.S. Food and Drug Administration, available at https://www.fda.gov/drugs/data-standards-manual-monographs/route-administration.

We agree that approval of certain parenteral neomycin sulfate products were withdrawn for safety reasons and unfavorable risk/benefit analyses. Systemic exposure to neomycin sulfate, whether resulting from intravenous or IM administration, or resulting from absorption after instillation in or irrigation of body cavities, structures or spaces, or from use in wet dressings may cause nephrotoxicity, irreversible ototoxicity (both auditory and vestibular), and neuromuscular blockade which may result in muscular paralysis or respiratory failure. Additionally, neomycin sulfate may result in cross-sensitization to other structurally similar aminoglycosides that are in clinical use for serious infections. The relevant references detailing the toxicities of parenteral neomycin sulfate through various routes of parenteral administration were cited in the July 27, 1979 *Federal Register* notice (44 FR 44180) and in the April 15, 1988 *Federal Register* final rule (53 FR 12644) and are included in the Reference List at the end of this document (1-12 and 13-30, respectively). Additional relevant references retrieved from a PubMed search that reported toxicities associated with systemic exposure to parenteral neomycin sulfate are also included in the Reference List (31-33).

We note that certain parenteral drug products containing neomycin sulfate were not withdrawn or removed from the market for safety reasons. The drug products containing neomycin sulfate with New Drug Application (NDA) or ANDA approvals currently in effect include parenteral formulations containing neomycin sulfate and other active ingredients for ophthalmic or otic use and formulations containing neomycin sulfate and other active ingredients for bladder irrigation. Neomycin sulfate products for bladder irrigation, are considered parenteral formulations but as explained below, bladder irrigation may be distinguished from other parenteral uses of neomycin sulfate that do not have a favorable risk/benefit profile.

Otic and Ophthalmic Use

Drug products in formulations containing neomycin sulfate and other active ingredients are approved and marketed for topical otic and ophthalmic use (drops and ointments). This use is generally for short durations and involves very small doses that result in negligible or no systemic exposure. A review of the literature did not identify a safety signal pertaining to neomycin sulfate systemic toxicities, especially hearing loss due to the otic formulations. The labeling does not carry a specific warning regarding the toxicity of neomycin sulfate (or of other components) if systemically absorbed, and the risk/benefit profile of these products/formulations is favorable.

Bladder Irrigation

Neomycin sulfate 40 mg/mL, in combination with polymyxin B sulfate 200,000 units per mL, is approved for irrigation of the intact bladder (ANDA 060707 (Neosporin G.U. Irrigant), ANDA 062664, ANDA 065106 and ANDA 065108, approved in 1966, 1986, 2006 and 2006 respectively). These products are indicated for short term use (less than 10 days) as continuous irrigants or rinse of the urinary bladder of abacteriuric patients to help prevent bacteriuria and Gram-negative septicemia associated with the use of indwelling catheters (see Appendix 20). The labeling for these products includes a Warning that they should not be given where there is a possibility of systemic absorption, and that they should not be used for irrigation other than the urinary bladder. The April 15, 1988 final rule (53 FR 12644) specifically addressed this product. The final rule stated that "approval of this fixed combination product does not provide the basis for approval of neomycin sulfate for prescription compounding for this indication. Efficacy of

the fixed combination, based upon the antimicrobial activities of specific concentrations of two antibiotics, is broader than that of each of the two active ingredients alone. The data used by the agency to conclude that Neosporin ® G. U. Irrigant is safe because it is not absorbed from the intact urinary bladder, and that it is effective as an irrigation solution, are different from the data that would be required to demonstrate the safety and effectiveness of a given concentration of neomycin sulfate as a single-ingredient irrigation preparation." The Agency also noted in the final rule that approval of this product is for use as an irrigation solution of the intact urinary bladder, where systemic absorption of the prepared solution is minimal, and that the concurrent or sequential use of neomycin sulfate and polymyxin B sulfate should be avoided in situations where systemic absorption may occur (see Appendix 20).

The reference for lack of appreciable systemic exposure following bladder irrigation with neomycin sulfate and polymyxin B sulfate where the bladder wall is intact was not cited in the notice (53 FR 12644), but the initial approval package for ANDA 60707 was retrieved. Systemic absorption was evaluated in five healthy subjects and was low. Peak neomycin sulfate level was 1.6 microgram and fell to 0.1 microgram by 6 hours after the infusion. An additional reference indicating very low systemic exposure was found in the literature (36).

However, although systemic exposure to neomycin sulfate resulting from irrigation of bladder without evidence of inflamed bladder wall is low, this exposure may be higher in patients with pre-existing renal impairment, or the elderly. A literature review retrieved reports of ototoxicity following bladder irrigation in four patients with end stage renal disease (37, 38).

> ***Question 2*:** Do you have reason to expect that the safety issues that were identified as having been associated with neomycin sulfate would be restricted to parenteral formulations or do you expect these safety issues would extend to other drug products containing neomycin sulfate (e.g., other formulations, routes of administration, or dosage forms)?

DAI Response:

DAI considers that the risk-benefit profile of drug products containing neomycin sulfate with NDA or ANDA approvals currently in effect that do not have parenteral routes of administration remains favorable although some of these formulations may be associated with adverse reactions identified with parenteral use of neomycin sulfate. The drug products containing neomycin sulfate with NDA or ANDA approvals currently in effect include formulations for oral administration and formulations containing neomycin sulfate and other active ingredients for dermatologic use.

<u>Oral Tablets and Oral Solution</u>
Oral neomycin sulfate tablets are approved in the United States as adjunctive therapy for hepatic coma (portal-systemic encephalopathy) and as adjunctive therapy for the suppression of intestinal bacterial flora of the colon, e.g., preoperative preparation of the bowel prior to abdominal surgery. Oral neomycin solution is approved in the United States as adjunctive therapy for hepatic coma (portal-systemic encephalopathy).

The approved labeling for oral neomycin sulfate (tablets and oral solution) includes a Boxed Warning and a section in Warnings and Precautions regarding significant systemic absorption that may result in neurotoxicity (including ototoxicity) and nephrotoxicity following oral use even when used at the recommended doses, and regarding neuromuscular blockade. Labeling states not to use neomycin sulfate for surgical irrigation, and states that neomycin sulfate is more toxic than other aminoglycosides. Labeling also states that irreversible cases of congenital deafness have been reported in infants born to women who had received streptomycin (another aminoglycoside) during pregnancy (see Appendices 18, 19).

In the consult provided below, the DHN conclude that the risk-benefit profile of oral neomycin sulfate (tablets and oral solution) for its approved indications remains favorable and that the product is adequately labeled. DAI also agrees that the risk/benefit profile for use of oral neomycin sulfate for adjunctive therapy for hepatic coma (portal-systemic encephalopathy) and as adjunctive therapy for the suppression of intestinal bacterial flora of the colon, e.g., preoperative preparation of the bowel prior to abdominal surgery remains favorable. To note, a retrospective analysis of colectomy data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) indicates that the use of oral antibacterial drugs (including neomycin sulfate) plus mechanical bowel preparation reduces the occurrence of surgical site infections and anastomotic leaks in bowel surgery (34).

Dermatologic Use

Drug products in formulations containing neomycin sulfate and other active ingredients are approved and marketed as topical ointment for dermatologic use for the treatment of minor wound infections. We note that dermatologic products administered topically are not considered to be administered parenterally. Similar to the otic and ophthalmic products, these are used for a short time and involve small doses. Systemic absorption may be theoretically possible for large open wounds. Review of the literature did not identify a safety signal pertaining to neomycin sulfate toxicities and labeling of the topical dermatologic products includes a Warning regarding ototoxicity. Our assessment is that the risk/benefit of these products is favorable if used as labeled.

> ***Question 3*:** Do you recommend that neomycin sulfate be included on the Withdrawn or Removed List and, if so, how should the entry be described? Please include your rationale for your recommendation.

DAI Response:

Yes, DAI recommends that all parenteral neomycin sulfate formulations, except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder, be included on the Withdrawn or Removed List. The rationale for limiting the listing was discussed in the responses to questions 1 and 2.

We recommend that the following entry for neomycin sulfate be added to the Withdrawn or Removed List:

Neomycin Sulfate: All parenteral drug products containing neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder).

III. DIVISION OF HEPATOLOGY AND NUTRITION (DHN), CDER

Evaluation of Parenteral Neomycin Sulfate for the Withdrawn or Removed List

FDA's Division of Hepatology and Nutrition (DHN) was asked to provide input on two questions related to whether neomycin sulfate should be included on the Withdrawn or Removed List, and if yes, on how the drug should be described on the list. The two questions and DHN's response are provided here.

> ***Question 1*:** Do you have reason to expect that the safety issues that were identified in the consult provided by the Division of Anti-Infectives as having been associated with neomycin sulfate would be restricted to parenteral formulations or do you expect these safety issues would extend to other drug products containing neomycin sulfate (e.g., other formulations, routes of administration, or dosage forms)? Provide an assessment on the safety of neomycin sulfate oral formulations.

DHN Response:

We have reviewed the consult provided by the DAI which identifies nephrotoxicity, irreversible ototoxicity (both auditory and vestibular), and neuromuscular blockade which may result in muscular paralysis or respiratory failure as having been associated with systemic exposure and indicates that the approval of certain parenteral neomycin sulfate drug products were withdrawn for safety reasons and unfavorable risk/benefit analyses.

Oral neomycin sulfate (tablets and oral solution) is approved in the United States as adjunctive therapy for hepatic coma (portal-systemic encephalopathy) and the approved labeling includes a Boxed Warning for neurotoxicity (including auditory ototoxicity and vestibular toxicity, neuromuscular blockade, and respiratory paralysis) and nephrotoxicity (see Appendices 18, 19). Oral neomycin sulfate tablets are also approved in the United States as adjunctive therapy for the suppression of intestinal bacterial flora of the colon, e.g., preoperative preparation of the bowel prior to abdominal surgery.

In any situation prior to a drug's approval or withdrawal, the Agency weighs the acceptability of the risks against the benefits and the risk/benefit analysis for a product may differ depending on factors such as the intended indication and patient population.

Oral neomycin sulfate is labeled appropriately for potential risks and with directions to the physician regarding increasing risks for toxicity with chronic dosing in patients who cannot be treated with a less toxic antibacterial drug. The label instructs physicians to monitor serum concentrations and for evidence of toxicity.

The use of oral neomycin sulfate still appears to have an acceptable risk/benefit ratio for its approved indications, and we see no reason to recommend its removal from the market for these indications.

> ***Question 2*:** Do you recommend that neomycin sulfate be included on the Withdrawn or Removed List and, if so, how should the entry, based on your assessment and evaluation of the oral formulations, be described? Should this proposed entry also include oral formulations? Please include your rationale for your recommendation.

DHN Response:

DHN agrees that all parenteral drug products containing neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder) should be included on the Withdrawn or Removed List. We do not believe it is appropriate to include the oral formulations on this list because oral neomycin sulfate formulations remain approved and marketed.

The currently marketed oral preparations have a low bioavailability (97% of the neomycin sulfate is not absorbed) and as such safety risks are lower than the parenteral dosing. The oral neomycin sulfate formulations have an acceptable risk/benefit profile for the hepatic encephalopathy indication (as discussed in the answer to question 1 above) and the current labeling carries adequate warnings about potential toxicities when used as labeled. However, if oral neomycin sulfate can be compounded into a parenteral injection or used as a liquid lavage parenteral formulation during intraoperative procedures (i.e., a liquid solution that is used to bathe an intrapleural or intraperitoneal surgical site), the same safety concerns associated with neomycin sulfate for injection would apply, as the delivery of oral neomycin sulfate compounded in a parenteral form would be expected to be associated with the same toxicities that prompted removal of the injection formulation, i.e., toxicities associated with via parenteral routes (intramuscular, intrapleural, intraperitoneal) and lavage due to higher systemic exposures associated with those delivery routes.

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APPENDIX 1:

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: May 5, 1970.

SAM D. FINE,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 70-5819; Filed, May 12, 1970; 8:45 a.m.]

[DESI 11267]

FLUOXYMESTERONE WITH ETHINYL ESTRADIOL

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug:

Fluoxymesterone 1.0 milligram with ethinyl estradiol 0.02 milligram, marketed as Halodrin Tablets, by The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49001 (NDA 11-267).

The drug is regarded as a new drug. The effectiveness classification and marketing status are described below.

A. *Effectiveness classification.* 1. The Food and Drug Administration has considered the Academy report and concludes that fluoxymesterone with ethinyl estradiol is probably effective for use in the treatment of senile and post-menopausal osteoporosis.

2. This drug is possibly effective for the treatment of the menopausal syndrome; male climacterium; and osteoporosis in certain patients following long-term adrenocorticoid therapy.

B. *Marketing status.* 1. Those indications for which the drug is described in paragraph A above as probably effective may continue to be used for 12 months, and the indications described as possibly effective may continue to be used for 6 months, following the date of this publication, to allow additional time within which holders of previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness.

2. At the end of the 6-month and 12-month periods, any such data will be evaluated to determine whether there is substantial evidence of effectiveness of the drug for such uses. The conclusions concerning the drug will be published in the FEDERAL REGISTER. If no studies have been undertaken or if the studies do not provide substantial evidence of effectiveness, procedures will be initiated to withdraw approval of the new-drug application for the drug, pursuant to the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act. Withdrawal of approval of the application will cause any such drugs on the market to be new drugs for which an approval is not in effect.

3. Within 60 days from publication hereof in the FEDERAL REGISTER the holder of any approved new-drug application for such drug is requested to submit a supplement to his application to provide for revised labeling, as needed, which, taking into account the comments of the Academy, furnishes adequate information for safe and effective use of the drug, is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970 (21 CFR 3.74), and recommends use of the drug as follows: (The possibly effective indications may also be included for 6 months).

INDICATIONS

Osteoporosis—senile and post menopausal.

The supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9 (d) and (e)), which permit certain changes to be put into effect at the earliest possible time, and the revised labeling should be put into use within the 60-day period.

The above named holder of the new-drug application for this drug has been mailed a copy of the NAS-NRC report. Any interested person may obtain a copy of this report by writing to the office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 11267 and be directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Requests for NAS-NRC report: Press Relations Office (CE-200).
Supplements (identify with NDA number): Office of Marketed Drugs (BD-200), Bureau of Drugs.
Original new-drug application: Office of New Drugs (BD-100), Bureau of Drugs.
All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: April 27, 1970.

SAM D. FINE,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 70-5820; Filed, May 12, 1970; 8:46 a.m.]

[DESI 7837]

NEOMYCIN SULFATE STERILE POWDER

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following preparations of neomycin sulfate sterile powder:

1. Mycifradin Sulfate; neomycin sulfate sterile powder 0.5, 5.0, or 10 grams per vial; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49001 (NDA 7-837).

2. Neomycin sulfate sterile powder, 0.5 or 5.0 grams per vial; Philadelphia Laboratories, Inc., 9815 Roosevelt Boulevard, Philadelphia, Pa. 19114 (NDA 11-596).

3. Neomycin sulfate sterile powder, 0.5 gram per vial; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 60-366).

4. Neomycin sulfate sterile powder, 0.5 or 5.0 grams per vial; Pure Laboratories, Inc., 50 Intervale Road, Parsippany, N.J. 07054.

The Food and Drug Administration concludes that when administered intramuscularly neomycin sulfate powder is probably effective for the indications described in the labeling guidelines in this announcement.

Preparations containing neomycin sulfate sterile powder are subject to the antibiotic certification procedures pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act. Batches of the drug for which certification is requested should provide for labeling information in accord with labeling guidelines developed on the basis of this reevaluation of the drug and published in this announcement.

The above named firms and any other holders of applications approved for a drug of the kind described above are requested to submit, within 60 days following publication of this announcement in the FEDERAL REGISTER, amendments to their antibiotic applications to provide for revised labeling. Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

WARNING

In Patients With Impaired Kidney Function or With Prerenal Azotemia, Systemic Use of Neomycin Sulfate May Result in Irreversible Deafness and/or Renal Damage, Even With Conventional Doses. Use Only With Extreme Caution in the Presence of Impaired Renal Function.

Parenteral neomycin sulfate should not be given concurrently or in series with other ototoxic and/or neurotoxic drugs such as streptomycin, kanamycin, polymyxin B, colistin and viomycin, because the toxicity may be additive.

The neurotoxicity of neomycin can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given to patients simultaneously receiving anesthetics or muscle relaxants.

DESCRIPTION

Neomycin sulfate is an aminoglycoside antibiotic produced from *Streptomyces fradiae* with broad spectrum antibacterial properties but high toxicity to the eighth nerve and the kidneys. (Additional descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

Neomycin is effective in vitro against gram-positive and gram-negative organisms, in concentrations of 5 to 10 mcg./ml. or less. The drug is well absorbed after intramuscular injection and widely distributed in body fluids and tissues. Injection of 300 mg. every 6 hours for four doses, followed by the same quantity every 12 hours, yields blood concentrations of 12–30 mcg./ml. in 48–72 hours. If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. disc should give a zone of 16 mm. or more when the organism is sensitive to neomycin.

From 30 to 50 percent of a parenteral dose is excreted in the urine.

INDICATIONS

Intramuscular use of neomycin sulfate should be restricted to hospitalized patients with severe systemic infections, due to the following organisms, when these are resistant to other less toxic antimicrobials but susceptible to neomycin: *Pseudomonas aeruginosa, H. influenzae, Klebsiella pneumoniae, P. vulgaris, E. coli, A. aerogenes.*

Neomycin sulfate has been successfully used in urinary tract infections due to susceptible pathogens, but should be reserved for cases in which no other antimicrobial agent is effective.

CONTRAINDICATIONS

Neomycin sulfate is contraindicated in patients known to be sensitive to it.

PRECAUTIONS

Neomycin sulfate is potentially nephrotoxic. Urinary examinations for albumin, casts and cells should be made before starting therapy and daily; BUN and audiometric determinations should also precede therapy and be repeated during neomycin sulfate administration. Inadequate renal function interferes with neomycin excretion, producing high blood levels which increase the risk of both ototoxicity and nephrotoxicity (see Warning above).

The possibility of acute toxicity increases in premature infants and neonates.

Avoid concurrent use of curariform muscle relaxant drugs and drugs which potentiate neuromuscular blocking effects (ether, tubocurarine, succinylcholine, gallamine, decamethonium and sodium citrate). If signs of respiratory paralysis appear, respiration should be assisted as required, and the drug discontinued.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

USAGE IN PREGNANCY

The safety of this drug in human pregnancy has not been established.

ADVERSE REACTIONS

Hypersensitivity reactions, primarily skin rashes, may occur with the use of neomycin sulfate.

DOSAGE AND ADMINISTRATION

Adults: 15 mg./kg./day in four equally spaced, divided doses. The total daily dose should not exceed one gram.

Premature and full-term newborn infants: 4 mg./kg./day, divided in four doses.

Older infants and children: 7.5–15 mg./kg./day, divided in four doses. Therapy should not be continued beyond ten days.

Preparation of solutions: Add sufficient sterile normal saline to the vial to prepare a concentration of 250 mg./ml. (E.g.: Add 2 cc. Sodium Chloride Injection U.S.P. to a 0.5 Gm. vial of dry powder.)

The Food and Drug Administration concludes that for the following labeled claims neomycin sulfate powder is possibly effective: active against many gram-negative and gram-positive bacteria; treatment (intraperitoneal instillation) of peritonitis and prevention of peritonitis following peritoneal contamination during surgery; for control of secondary infections of mycotic lesions due to neomycin-sensitive bacteria; for use as wet dressings, packs, or irrigations in secondarily infected wounds and ulcers, varicose ulcers, and affections of the eye such as conjunctivitis, blepharitis, and sty; adjuvant therapy for impetigo and other pyogenic or secondarily infected dermatoses; for suppression of bacterial growth in the bowel; for treatment of trophic ulcers and secondarily infected burn areas; and for intestinal instillation in emergency abdominal surgery.

Batches of the drug which bear labeling with indications regarded as probably or possibly effective and otherwise in accord with the labeling conditions herein will be accepted for release or certification by the Food and Drug Administration for a period of 12 months for probably effective claims and 6 months for possibly effective claims, from the publication date of this announcement to allow any applicant to obtain and submit data to provide substantial evidence of effectiveness of the drug for use in such conditions.

The Food and Drug Administration regards neomycin sulfate powder as lacking substantial evidence of effectiveness for the following claims: relatively nonirritating and low index of sensitivity; micro-organisms do not readily develop resistance to neomycin; prophylaxis against infection incident to cystoscopy and retrograde pyelography; prevention of postcatheterization sepsis or a postinstrumental reaction; for the treatment of nonspecific urethritis; and for use following transurethral resection. Preparations containing the drug with labeling bearing these claims will no longer be acceptable for certification or release after the publication date of this announcement.

Any person who would be adversely affected by deletion of the claims for which the drug lacks substantial evidence of effectiveness, as described in this announcement, may, within 30 days following the publication date hereof, submit comments or pertinent data bearing on the effectiveness of the drug for such use. To be considered acceptable for review, the data must be well-organized and consist of adequate and well-controlled studies not previously submitted.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth in this announcement. Requests for such meetings should be made to the Division of Anti-Infective Drugs (BD–140), at the address given below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

A copy of the NAS-NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 7837 and be directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Requests for NAS-NRC Report: Press Relations Office (CE–200).

Amendments (Identify with NDA number): Division of Anti-Infective Drugs (BD–140), Office of New Drugs, Bureau of Drugs.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD–201), Bureau of Drugs.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050–51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: May 4, 1970.

SAM D. FINE,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 70–5818; Filed, May 12, 1970; 8:45 a.m.]

[DESI 12019]

PAROMOMYCIN SULFATE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following antibiotic drugs for oral use:

1. Paromomycin sulfate, marketed as Humatin Kapseals containing the equivalent of 250 mg. paromomycin base per capsule (NDA 12–019); and

2. Paromomycin sulfate, marketed as Humatin Syrup Pediatric, containing the equivalent of 125 mg. paromomycin base per 5 ml. (NDA 12–790); both marketed by Parke, Davis and Co., Joseph Campau at the River, Detroit, Mich. 48232.

The Food and Drug Administration concludes that paromomycin sulfate is effective for acute and chronic intestinal amebiasis, and as adjunctive therapy in the management of hepatic coma.

Preparations containing paromomycin sulfate are subject to the antibiotic certification procedures pursuant to section

APPENDIX 2:

their average share of soluble coffee production in the United States. U.S. manufacturers of soluble coffee wishing to share in the special allocation are requested to supply the following information for the calendar years 1970 and 1971, separately:

1. Pounds of green coffee roasted by the respondent for the production of soluble coffee in the United States.

2. Location of plant or plants at which the above coffee was roasted.

The accuracy of such information must be certified by an authorized officer of the respondent subject to the penalties provided in 18 U.S.C. 1001 for making any false statements in any matter within the jurisdiction of a Department of the United States. Information so provided will be made available to the public for inspection and transmitted to the Government of Brazil as a basis for its allocations. In order that the information can be forwarded to the Government of Brazil as soon as possible, it must be received by certified mail no later than 15 working days from the date of publication of this notice in the FEDERAL REGISTER. Responses should be addressed to:

OIP 280, U.S. Department of Commerce, Washington, D.C. 20230. Attention: Coffee.

Dated: February 22, 1972.

STANLEY NEHMER,
Deputy Assistant Secretary for Resources, U.S. Department of Commerce.

[FR Doc.72-3002 Filed 2-28-72;8:49 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 7837]

NEOMYCIN SULFATE STERILE POWDER

Drugs for Human Use; Drug Efficacy Study Implementation; Follow-up Notice

In a notice (DESI 7837) published in the FEDERAL REGISTER of May 13, 1970 (35 F.R. 7464), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Mycifradin Sulfate containing neomycin sulfate sterile powder; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49001 (NDA 7-837).

2. Neomycin sulfate sterile powder; Philadelphia Laboratories, Inc., 9815 Roosevelt Boulevard, Philadelphia, Pa. 19114 (NDA 11-596).

3. Neomycin sulfate sterile powder; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 60-366).

4. Neomycin sulfate sterile powder; Pure Laboratories, Inc., 59 Intervale Road, Parsippany, N.J. 07054 (No. NDA number).

The notice stated that the drugs were regarded as probably effective, possibly effective, and lacking substantial evidence of effectiveness for the various labeled indications.

Based upon a reevaluation of these preparations, the Commissioner finds it appropriate to amend the announcement of May 13, 1970, as follows:

1. The effectiveness classification of the following indications is changed from probably effective to effective: For intramuscular use in the treatment of urinary tract infections due to susceptible strains of the following organisms: *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli,* and *Enterobacter aerogenes.*

2. The labeling guidelines are changed to read as follows:

NEOMYCIN SULFATE STERILE POWDER FOR INTRAMUSCULAR USE ONLY

WARNING

In Patients With Impaired Kidney Function or With Prerenal Azotemia, Systemic Use of Neomycin Sulfate May Result in Irreversible Deafness and/or Renal Damage, Even With Conventional Doses. Use Only With Extreme Caution in the Presence of Impaired Renal Function.

Parenteral neomycin sulfate should not be given concurrently or in series with other ototoxic and/or neurotoxic drugs such as streptomycin, kanamycin, polymyxin B, colistin and viomycin, because the toxicity may be additive.

The neurotoxicity of neomycin can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given to patients simultaneously receiving anesthetics or muscle relaxants.

Usage in Pregnancy

The safety of this drug in human pregnancy has not been established.

DESCRIPTION

Neomycin is an antibiotic obtained from the metabolic products of the actinomycete *Streptomyces fradiae.*

ACTIONS

(Data on absorption, metabolism, and antimicrobial activity to be supplied by the manufacturer. All quantitative references to the drug should be qualified by appropriate nomenclature, e.g. neomycin sulfate or neomycin base.)

If the Kirby-Bauer method of disc susceptibility is used, a 30 mcg. disc should give a zone of 17 mm. or more when the organism is susceptible to neomycin.

INDICATIONS

Neomycin sulfate may be indicated in treatment of urinary tract infections due to susceptible strains of the following organisms: *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli,* and *Enterobacter aerogenes.* Because of its potential toxicity it should be reserved for hospitalized cases in which no other antimicrobial agent is effective.

CONTRAINDICATIONS

Neomycin sulfate is contraindicated in patients known to be sensitive to it.

WARNINGS

(See "Warning" box.)

PRECAUTIONS

Neomycin sulfate is potentially nephrotoxic. Urinary examinations for albumin, casts, and cells should be made before starting therapy and daily; BUN and audiometric determinations should also precede therapy and be repeated during neomycin sulfate administration. Inadequate renal function interferes with neomycin excretion, producing high blood levels which increase the risk of both ototoxicity and nephrotoxicity (see "Warning" box).

The possibility of acute toxicity increases in premature infants and neonates.

Avoid concurrent use of curariform muscle relaxant drugs and drugs which potentiate neuromuscular blocking effects (ether, tubocurarine, succinylcholine, gallamine, decamethonium and sodium citrate). If signs of respiratory paralysis appear, respiration should be assisted as required, and the drug discontinued.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

ADVERSE REACTIONS

Hypersensitivity reactions, primarily skin rashes, have been reported. Irreversible deafness and/or renal damage have been reported following extended and/or high dosage therapy with neomycin sulfate.

DOSAGE AND ADMINISTRATION

TO BE ADMINISTERED INTRAMUSCULARLY ONLY

Therapy should not be continued beyond 10 days. The total daily dose should not exceed 1 gram of neomycin sulfate.

Adults. 15 mg. neomycin sulfate/kg./day, divided in four equally spaced doses.

Premature and full-term newborn infants. 4 mg. neomycin sulfate/kg./day, divided in four equally spaced doses.

Older infants and children. 7.5-15 mg. neomycin sulfate/kg./day, divided in four equally spaced doses.

Preparation of solutions: To be supplied by manufacturer.

HOW SUPPLIED

To be supplied by the manufacturer.

Batches of the drug for which certification is requested should provide for labeling information in accord with labeling guidelines developed on the basis of this reevaluation of the drug and published in this announcement.

The remaining probably effective indication and the possibly effective indications have been reclassified as lacking substantial evidence of effectiveness in that no new evidence of effectiveness of this drug has been submitted pursuant to the notice of May 13, 1970. No effective indications remain for other than the intramuscular route of administration.

Batches of such drugs with labeling bearing indications for which substantial evidence of effectiveness is lacking are no longer acceptable for certification or release. Packages containing 5 or 10 grams of sterile powder are considered inappropriate sizes for preparation of

solutions for intramuscular administration and will no longer be certified or released.

Any person who will be adversely affected by the deletion from labeling of the indications for which the drug has been reclassified from probably or possibly effective to lacking substantial evidence of effectiveness may, within 30 days after the date of publication of this notice in the FEDERAL REGISTER, petition for the issuance of a regulation providing for other certification of the drug for such indications. The petition must be supported by a full factual and well documented medical analysis which shows reasonable grounds for the issuance of such regulation.

A petition for issuance of said regulation should be filed (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51 as amended, 59 Stat. 463 as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: February 17, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-2966 Filed 2-28-72;8:46 am]

Office of the Secretary

OFFICE OF SAFETY MANAGEMENT

Statement of Organization, Functions, and Delegation of Authority

The Statement of Organization, Functions, and Delegations of Authority of the Department is amended to establish the Office of Safety Management under the Assistant Secretary for Administration and Management.

The following new section is added to Chapter 1-U "The Assistant Secretary for Administration and Management", to read as follows:

SECTION 1U011001: The Office of Safety Management, headed by a Director reports to the Deputy Assistant Secretary for Administration, and is responsible for the management of a Department-wide occupational safety and health program in accordance with section 7902 of title 5 United States Code, section 19(a) of the Occupational Safety and Health Act of 1970, and section 1 of Executive Order 11612. Specifically this office:

Develops and promulgates plans, policies, standards, and procedures for the Department-wide Safety Program;

Represents the Department on the Federal Safety Advisory Council, Federal Fire Council, and provides official Department representation to the Department of Labor, General Services Administration and other Federal agencies;

Provides Department liaison with the National Fire Protection Association, National Safety Council, and other outside organizations;

Advises top management of the Department on all matters pertaining to the management and direction of the Department Safety Program and provides technical assistance to the operating agencies, regional offices, and field installations in all areas of safety management;

Plans and administers a Safety Management Information System;

Coordinates safety education and training activities throughout the Department;

Prepares the Department's position on proposed legislation concerning safety and fire protection; and

Coordinates and monitors research for development of new accident prevention methods and concepts.

Dated: February 18, 1972.

RODNEY H. BRADY,
Assistant Secretary for Administration and Management.

[FR Doc.72-2968 Filed 2-28-72;8:46 am]

Social Security Administration

GUYANA

Notice of Finding Regarding Foreign Social Insurance or Pension System

Section 202(t)(1) of the Social Security Act (42 U.S.C. 402(t)(1)) prohibits payment of monthly benefits to aliens, subject to the exceptions described in sections 202(t)(2) through 202(t)(5) of the Social Security Act (42 U.S.C. 402(t)(2) through 402(t)(5)), for any month after they have been outside the United States for 6 consecutive calendar months.

Section 202(t)(2) of the Social Security Act (42 U.S.C. 402(t)(2)) provides that section 202(t)(1) shall not apply to any individual who is a citizen of a foreign country which the Secretary of Health, Education, and Welfare finds has in effect a social insurance or pension system which is of general application in such country and under which (A) periodic benefits, or the actuarial equivalent thereof, are paid on account of old age, retirement, or death, and (B) individuals who are citizens of the United States but not citizens of such foreign country and who qualify for such benefits are permitted to receive such benefits or the actuarial equivalent thereof while outside such foreign country without regard to the duration of the absence.

Pursuant to authority duly vested in the Commissioner of Social Security by the Secretary of Health, Education, and Welfare, and redelegated to him, the Director of the Bureau of Retirement and Survivors Insurance has approved a finding that Guyana beginning September 29, 1969, has a social insurance system of general application which pays periodic benefits on account of old age, retirement, or death, and under which citizens of the United States, not citizens of Guyana, who leave Guyana, are permitted to receive such benefits or their actuarial equivalent at the full rate without qualification or restriction while outside that country.

Accordingly, it is hereby determined and found that Guyana has in effect beginning with September 29, 1969, a social insurance system which meets the requirements of section 202(t)(2) of the Social Security Act (42 U.S.C. 402(t)(2)).

This revises the finding with respect to Guyana published in the FEDERAL REGISTER of April 5, 1967 (32 F.R. 5592).

Dated: February 18, 1972.

HUGH F. MCKENNA,
Director, Bureau of Retirement and Survivors Insurance.

[FR Doc.72-3027 Filed 2-28-72;8:51 am]

ATOMIC ENERGY COMMISSION

[Dockets Nos. 50-373, 50-374]

COMMONWEALTH EDISON CO.

Notice of Availability of Applicant's Supplemental Environmental Reports

Pursuant to the National Environmental Policy Act of 1969 and the Atomic Energy Commission's regulations in Appendix D to 10 CFR Part 50, notice is hereby given that "Supplements 1 and 2 to Environmental Report for La Salle County Station Units 1 and 2," dated January 17, 1972, and February 14, 1972, respectively, by the Commonwealth Edison Co. are being placed in the Commission's Public Document Room at 1717 H Street NW., Washington, DC, and in the Reddicks Public Library, 100 West Lafayette Street, Ottawa, IL 61350. The supplements are also being made available at the Office of Planning and Analysis, Executive Office of the Governor, Room 614, State Office Building, Springfield, Ill. 62706. Supplement 1, consisting of page changes, in addition to Supplement 2, a report, update and provide supplemental information to the Environmental Report for the proposed construction of the La Salle County Nuclear Power Station Units 1 and 2 to be located in Brookfield Township, La Salle County, Ill. Notice of availability of the applicant's report entitled "Environmental Report for La Salle County Station Units 1 and 2," dated November 4, 1971, was published in the FEDERAL REGISTER on January 22, 1972 (37 F.R. 1073).

After these supplements have been analyzed by the Commission's Director of Regulation or his designee, a draft detailed statement of environmental considerations will be prepared. Upon preparation of the draft detailed statement, the Commission will, among other things, cause to be published in the FEDERAL REGISTER a summary notice of availability of the draft detailed statement. The summary notice will request comments from interested persons on the proposed action and on the draft statement. The summary notice will also contain a statement to the effect that the comments of Federal Agencies and State and local officials will be available when received.

Dated at Bethesda, Md., this 22d day of February 1972.

APPENDIX 3:

§ 19.45 Transfer of merchandise, approval and method.

Approval of the application by the district director shall serve as a permit to transfer the container and its contents to the station. The merchandise may only be transferred to a container station by a bonded cartman or bonded carrier. The cartman or carrier shall receipt for the merchandise on both copies of the application.

(Secs. 551, 565, 46 Stat. 742, as amended, 747 as amended; 19 U.S.C. 1551, 1565)

§ 19.46 Employee lists.

A permit shall not be granted to an operator to transfer a container or containers to a container station, if the operator, within 30 calendar days after the date of receipt of a written demand by the district director, does not furnish a written list of names, addresses, social security numbers, and dates and places of birth of persons employed by him in connection with the movement, receipt, storage or delivery of imported merchandise. Having furnished such a list, no new permit shall be issued to an operator who has not within 10 calendar days after the employment of any new personnel employed in connection with the movement, receipt, storage, or delivery of imported merchandise advised the district director in writing of the names, addresses, social security numbers, and dates and places of birth of such new employees. The operator shall, within 10 calendar days, advise the district director if the employment of any employee is terminated. A person shall not be deemed to be employed by an operator if he is an officer or employee of an independent contractor engaged by the operator to move, receive, store, deliver, or otherwise handle imported merchandise.

(Sec. 624, 46 Stat. 759; 19 U.S.C. 1624)

§ 19.47 Security.

The space to be used for the purposes of breaking bulk and delivering cargo shall be properly secured against access by unauthorized persons, including persons not on the list of current employees furnished to the district director by the container station operator, the principal on the bond, as required by § 19.46. A suitable working and office space for the use of Customs officers and employees performing functions in the area shall also be provided.

(Sec. 624, 46 Stat. 759; 19 U.S.C. 1624)

§ 19.48 Withdrawal of privileges.

If discrepancies are discovered which indicate that the revenue may be endangered or there is a failure to retain or secure the designated examination packages, the privileges of a container station operator granted by this subpart may be revoked pursuant to the procedure stated in § 19.3(e).

(Sec. 624, 46 Stat. 759; 19 U.S.C. 1624)

§ 19.49 Entry of containerized merchandise.

Merchandise not entered within the lay order period, or extension thereof, shall be placed in general order. The importing carrier shall issue carrier's certificates for individual shipments in a container. Entries covering merchandise transferred to a container station shall clearly show that the merchandise is at the container station.

(Sec. 484, 46 Stat. 722, as amended; 19 U.S.C. 1484)

(R.S. 251, as amended, secs. 555, 556, 624, 644, 46 Stat. 743, as amended, 759, 761; 19 U.S.C. 66, 1551, 1556, 1624, 1644)

[FR Doc.72-3016 Filed 2-28-72;8:51 am]

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

[DESI 7837]

PART 148i—NEOMYCIN SULFATE

Neomycin Sulfate Sterile Powder

In a notice (DESI 7837) published in the FEDERAL REGISTER of May 13, 1970 (35 F.R. 7837), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Mycifradin Sulfate containing neomycin sulfate sterile powder; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49001 (NDA 7-837).

2. Neomycin sulfate sterile powder; Philadelphia Laboratories, Inc., 9815 Roosevelt Boulevard, Philadelphia, Pa. 19114 (NDA 11-596).

3. Neomycin sulfate sterile powder; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 60-366).

4. Neomycin sulfate sterile powder; Pure Laboratories, Inc., 59 Intervale Road, Parsippany, N.J. 07054 (No NDA number).

The notice stated that the drugs were regarded as probably effective, possibly effective, and lacking substantial evidence of effectiveness for the various labeled indications. In a notice published elsewhere in this issue of the FEDERAL REGISTER, the Food and Drug Administration announces that these claims have been reevaluated. As a result of this reevaluation, no effective indications remain for other than the intramuscular route of administration and packages containing 5 or 10 grams of sterile powder are not appropriate for preparation of solutions for intramuscular administration. Accordingly, the Commissioner concludes that the antibiotic drug regulations should be amended to reflect these conclusions.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51 as amended, 59 Stat. 463 as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner (21 CFR 2.120), Part 148i is amended in § 148i.1 by revising paragraph (a)(2) to read as follows:

§ 148i.1 Neomycin sulfate.

(a) * * *

(1) * * *

(2) *Packaging.* In addition to the requirements of § 148.2 of this chapter, each immediate container shall contain 0.35 gram of neomycin.

* * * * * *

Any person who will be adversely affected by this amendment to the antibiotic drug regulations may file objections to this order requesting a hearing and showing reasonable grounds for the hearing. The statement of reasonable grounds and request for a hearing shall be submitted in writing within 30 days after publication hereof in the FEDERAL REGISTER, shall state the reasons why the antibiotic drug regulations should not be so amended, and shall include a well organized and full factual analysis of the clinical and other investigational data the objector is prepared to prove in support of his objections.

A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing. When it clearly appears from the data incorporated into or referred to by the objections and from the factual analysis in the request for a hearing that no genuine issue of fact precludes the action taken by this order, the Commissioner will enter an order making findings and conclusions on such data.

If a hearing is requested and justified by the objections, the issues will be defined and a hearing examiner named to conduct the hearing. The provisions of Subpart F of 21 CFR Part 2 shall apply to such hearing, except as modified by 21 CFR 146.1(f), and to judicial review in accord with section 701 (f) and (g) of the Federal Food, Drug, and Cosmetic Act (35 F.R. 7250, May 8, 1970).

Objections and requests for a hearing should be filed (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852. Received objections and requests for a hearing may be seen in the above office during regular business hours, Monday through Friday.

Effective date. This order shall become effective 40 days after its date of publication in the FEDERAL REGISTER. If objections are filed, the effective date will be extended for ruling thereon. In so ruling, the Commissioner will specify another effective date.

Dated: February 17, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-2965 Filed 2-28-72;8:49 am]

APPENDIX 4:

SUMMARY MINUTES
ANTI-INFECTIVE AGENTS ADVISORY COMMITTEE

Nineteenth Meeting
April 4-5, 1977

Parklawn Building
Rockville, Maryland

CHAIRMAN

Monto Ho, M.D.

EXECUTIVE SECRETARY

Mary K. Bruch

MEMBERS

Theodore Eickhoff, M.D.
Henry Shinefield, M.D.
Jay Sanford, M.D. (April 4, only)
Frederick Rapp, Ph.D.
Lauri Thrupp, M.D.
Paul Lietman, M.D., Ph.D. (absent)
Vevyl Greene, Ph.D. (absent)

FDA PERSONNEL

Merle L. Gibson, M.D. - Director
Division of Anti-Infective Drug Products

Jose Canchola, M.D. - Medical Officer
Division of Anti-Infective Drug Products

Theresa Reed, M.D. - Group Leader
Division of Anti-Infective Drug Products

SUMMARY MINUTES

The nineteenth meeting of the Anti-Infective Agents Advisory Committee was held on April 4-5, 1977. All sessions of this meeting were open. There was no response to the Chairman's invitation for public participation.

Open Committee Deliberations

Bacteremia and Septecemia

The Committee was provided with conventional definitions and labeling claims and asked their view of the meaning and distinction, if it exists, between the two words. The need for requesting this distinction arose when a sponsor requested that a specific cephalosporin be labeled for bacteremia when the term used for most drugs indicated for infection of the bloodstream is septicemia.

After considerable discussion, the Committee concluded that the most desirable general term is septicemia including as it does the implication of the presence of microbial products

as well as microorganisms. However as infection patterns continue to change, the more useful term may be bacterial septicemia to distinguish from a fungal or viral septicemia. The Committee recommended that there be an effort to have septicemia or bacterial septicemia used across the board in all labeling.

Neomycin

Discussion of Proposed Decertification of a Sterile Vial for Parenteral Use (IM Injection)

This is a currently marketed dosage form of neomycin although, after the DESI publications on this drug, only one indication remains. This if for use in urinary tract infections where other antibiotics are not effective. It is apparant that some portion of the drug that is certified is used for irrigation although there is no labeling indication for such a use. In fact the DESI announcement has downgraded this dosage form for this indication as showing no substantial evidence of effectiveness. The Committee was quite concerned about possible unlabeled use fearing possible toxicity. Since

they believed that there is essentially no use of the dosage form for the labeled indication, the Committee concluded that the risk/benefit judgement did not warrant continued marketing. They unanimously recommended that the dosage form no longer be certified. They believed that considering the potential toxicity, other drugs with less toxicity are available for the single labeled use.

Neomycin

Use of Non-Sterile Bulk for Prescription Compounding

This form of neomycin is supplied in bulk form in non-sterile 100 mg vials. There is no labeling for this dosage form. It is used by hospital pharmacies and others to formulate a number of other dosage forms.

One firm supplying this drug has suggested to FDA that it be accompanied by a warning label. Neither the types of dosage forms nor concentration can be controlled and toxic effects have occurred from its use. Some compounders wishing to formulate neomycin have used the parenteral vial discussed above to avoid the necessity of sterilization before use as an irrigant.

Some members felt that the risk associated with the uses of the bulk as an irrigant would be reduced if instructions were given to reduce the level of neomycin. Since effectiveness studies are not available for any concentration of neomycin, this alternative was not recommended.

The Committee concluded that a warning label should be placed on this neomycin product immediately. Committee members will frame a black box warning. Firms manufacturing the product will be notified to add the warning and will be on notice that since there is no evidence of effectiveness for the common uses, data will be required.

Intrathechal Administration of Gentamicin

There is no labeling on the parenteral dosage form of gentamicin for intrathechal administration, although it is widely used by this route in serious cases of meningitis. Dr. Reed reviewed the application for a special dosage form without preservatives for this use. A controlled study in neonatal meningitis showed that when administered by the intralumbar route the drug was not effective. Dr. Reed explained what she felt the difficulties were with the study with this

route of administration. She felt that the drug did not reach site of infection. She pointed out the anatomical reasons for this and also for possible ototoxic effects if the direct intraventricular route for intrathecal administration is not carefully controlled.

A new study is underway in neonatal meningitis at a higher dose and with intraventriacular administration. Assuming that the new study will be successful, the Committee was asked whether a study of effectiveness by the intraventricular route in adult meningitis should be performed.

The Committee discussed the incidence and the number of available patients for such a study. They concluded that the intrathecal route is almost always used in adult infections and that without it, there would be essentially a zero cure rate. The Committee concluded that this information could be derived from an examination of historical controls and already submitted cases.

The Committee recommended that before any further studies are recommended, the cases in the NDA submission be thoroughly

examined and the Pseudomonas meningitis infections be extracted and examined for effectiveness. They believed if this process showed that the preserved form of the drug is effective in these cases, the unpreserved product could be labeled for this indication.

However this procedure will not resolve the difference in effectiveness between intralumbar and intraventricular administration. The Committee felt that animal studies should be pursued to determine the toxicity of gentamicin to the inner ear if it is exposed during intraventricular administration of the drug.

Chemical Synovitis Resulting from Intra-Auricular Injection of Penicillin

One physician, Dr. Lichtor, has corresponded with DAIDP for several years feeling that there should be a warning in the labeling against intrauricular use of penicillin. However, after review of references and the material submitted, the Committee concluded that a discussion of the problem in a physicians drug bulletin would be more useful. They did not believe the problem is common enough for a warning and felt that most physicians

are aware of the problem. They felt that there is also the possibility of interpretation of a prohibition in the labeling as an invitation to use penicillin in this way. They recommended that a letter be sent thanking Dr. Lichtor for his interest and stating the Committee's conclusions.

Antiviral Drug Guidelines for Investigation

Dr. Jose Canchola, reviewed the various types of antiviral drugs being investigated and described the stage of investigation each one is in. This was a follow-up of a previous presentation. Dr. Canchola brought the Committee up-to-date and initiated discussion of guidelines for in vitro testing of antiviral drugs (see attachments). He said that some uniform requirements are essential particularly for preclinical investigation. Since the mode of action of these drugs differs, hard and fast requirements are difficult to enforce across the board and still permit submission of sufficient data to assess the toxicity of a specific drug. The Pharmacology/Toxicology Advisory Committee for the Bureau will review the animal

toxicology requirements but the Anti-Infective Agents Committee will have to compile the completed guidelines, including in vitro (and also cytotoxicity studies) and in vivo animal and human clinical studies. After a discussion of how the Committee should proceed to complete this important task, they decided that a sub-committee should initiate the work. With this in view, Dr. Fred Rapp and Dr. Canchola will prepare a second draft of the outline for in vitro studies presented to the Committee at this meeting.

The next meeting was set for November 14-15, 1977.

Prepared By:

Mary K. Bruch

Mary K. Bruch
Executive Secretary

I certify that I attended the Nineteenth Meeting of the Anti-Infective Agents Advisory Committee meeting on April 4-5, 1977 and that these minutes accurately reflect what transpired.

Monto Ho M.D.

Chairman
Monto Ho, M.D.

APPENDIX 5:

the revocations and of the details of the recall request.

Neomycin sulfate for prescription compounding is only one of several neomycin sulfate preparations made available through the certification process. Other preparations, including otic, ophthalmic, oral, and dermatologic dosage forms, continue to be regularly certified and marketed and are not affected by this proposal.

The agency has determined that this document does not contain an agency action covered by § 25.1(b) (21 CFR 25.1(b)) and, therefore, consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 444 be amended by revoking and reserving § 444.942a *Neomycin sulfate for prescription compounding.*

Interested persons may, on or before September 25, 1979, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Interested persons may, also, on or before August 27, 1979, submit to the Hearing Clerk (address above) a request for an informal conference. The participants in an informal conference, if one is held, will have until August 27, 1979, or 15 days from the day of the conference, whichever is later, to submit their comments.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 17, 1979.

J. Richard Crout,

Director, Bureau of Drugs.

[FR Doc. 79-22889 Filed 7-26-79; 8:45 am]

BILLING CODE 4110-03-M

[21 CFR Part 444]

[Docket No. 79N-0151]

Certification of Sterile Neomycin Sulfate for Parenteral Use; Proposed Revocation of Provisions

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration proposes to amend the antibiotic regulations to revoke provisions for certification of neomycin sulfate in sterile vials for parenteral use. This action is being taken on the basis of widespread evidence that the drug's risks outweigh its benefit. This action would remove these drug products from the market.

DATES: Comments by September 25, 1979; requests for informal conference by August 27, 1979. FDA proposes that the final regulation based on this proposal become effective 60 days after the date of its publication in the Federal Register.

ADDRESS: Written comments or requests for an informal conference to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Merle Gibson, Bureau of Drugs (HFD–140), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4310.

SUPPLEMENTARY INFORMATION: FDA is proposing to revoke the regulation providing for certification of sterile neomycin sulfate for parenteral use.

Neomycin sulfate was discovered in 1949 when Waksman and Lechevalier isolated a soil organism, *Streptomyces fradiae*, which produced a new antibiotic containing a group of antibacterial substances. When purified, it was found to be a complex of three compounds, neomycins A, B, and C. Each compound demonstrated its own antibacterial activity. Commercial neomycin preparations consist primarily of neomycin B.

Before 1970, the approved labeling of neomycin sulfate indicated the drug for a number of uses, including:

(1) Intramuscular use (as an injectable) in certain serious systemic infections and urinary tract infections;

(2) Intraperitoneal instillation in treating peritonitis and preventing peritonitis following peritoneal contamination during surgery;

(3) Topical use in dressings, packs, and irrigations; and

(4) Intestinal instillation in emergency abdominal surgery.

The pre-1970 labeling for neomycin sulfate warned of the drug's potential ototoxicity (predominantly auditory toxicity or hearing loss) and nephrotoxicity (kidney damage).

On May 13, 1970 (35 FR 7464) and Februrary 29, 1972 (37 FR 4224), notices pertaining to neomycin sulfate sterile powder were published in the Federal Register as a result of the Drug Efficacy Study Implementation (DESI 7837).

The May 1970 notice announced FDA's conclusions regarding certain preparations of neomycin sulfate sterile powder reviewed by the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group and provided an opportunity for comment and for submission of pertinent data to support the indications.

The February 1972 notice amended the earlier notice as a result of a reevaluation of the antibiotic drug preparations involved. The 1970 notice as amended by the 1972 notice included findings that:

1. Neomycin sulfate sterile powder is effective for intramuscular use in the treatment of urinary tract infections due to susceptible strains of certain organisms *(Psuedomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli,* and *Enterobacter aerogenes).*

2. The drug lacks substantial evidence of effectiveness for all other labeling claims. These include: treatment of peritonitis (intraperitoneal instillation) and prevention of peritonitis following peritoneal contamination during surgery; for use as wet dressings, packs, or irrigations in secondarily infected wounds and ulcers, varicose ulcers, and infections of the eye; and for intestinal instillation in emergency abdominal surgery.

3. Labeling for the remaining marketed preparations should include a "Box Warning" and statements in the "Precautions" and "Adverse Reactions" sections emphasizing the potential nephrotoxic and ototoxic effects of neomycin sulfate and its potential for causing respiratory paralysis from neuromuscular blockade.

4. Previously marketed package sizes of 5 and 10 grams of sterile powder are inappropriate for preparation of solutions for intramuscular

administration. A separate regulation published in the Federal Register of February 29, 1972 (37 FR 4188), amended the provision for certification of sterile neomycin sulfate, § 148i.1 (21 CFR 148i.1, later recodified as § 444.42a (21 CFR 444.42a) in the Federal Register of May 30, 1974 (39 FR 18922)), to restrict the vial size to 0.35 gram (g) of neomycin.

In summary, based on the agency's conclusions after evaluation of NAS/NRC reports, the approved labeling for neomycin sulfate sterile powder was restricted to intramuscular administration for the treatment of certain urinary tract infections. Additionally, because of the drug's toxicity, the labeling stated that the drug should be reserved for hospitalized cases in which no other antimicrobial agent is effective. As a result of these procedures only a small vial size, 0.35 g neomycin per vial, was allowed to remain on the market.

Certain other neomycin sulfate preparations were not affected by the provisions of the February 1972 regulation. These include products for dermatologic use that are currently under review (and were discussed in the preamble to the proposal to establish a monograph for over-the-counter (OTC) topical antibiotic drug products published in the Federal Register of April 1, 1977 942 FR 17642)) and nonsterile neomycin sulfate for prescription compounding, a preparation available in containers of 10 to 100 g that has been used for the extemporaneous compounding of dermatologic drug products. A proposal to revoke certification for this preparation is published elsewhere in this issue of the Federal Register.

In light of clinical evidence that significant amounts of neomycin sulfate are systemically absorbed following dosing by most routes of administration, and, particularly, that neomycin sulfate has induced significant toxicity by the various parenteral routes (intramuscular, intrapleural, intraperitoneal, etc.), the agency has become increasingly concerned about the continued availability of sterile neomycin sulfate for parenteral use. The ototoxicity and nephrotoxicity due to neomycin sulfate is now well established (Refs. 1 through 7, 9, and 12 through 17). These toxicities may or may not be dose related and no safe parenteral dosage regimen has been recognized (Ref. 7). Moreover, neomycin sulfate, an aminoglycoside, is more toxic than other members of that chemical group, e.g., gentamicin, kanamycin, and streptomycin sulfates (Refs. 3 and 12). The drug causes cochlear damage that is manifest histologically by destruction of both inner and outer hair cells. It may also block the efferent synapsis. Ototoxicity is progressive to involve the entire auditory frequency range. It can occur abruptly or insidiously, at doses as low as 2 g, and may progress days, weeks, and even months after discontinuation of the drug (Refs. 1, 4, 7, 9, and 12). Although nephrotoxicity is often reversible after dosing, ototoxicity caused by neomycin sulfate is irreversible (Refs. 1, 2, 4, 9, 12, and 14). Neomycin ototoxicity is additive to the ototoxicity of other aminoglycosides and other ototoxic drugs (Refs. 7 and 9).

Neomycin sulfate is a potent producer of neuromuscular paralysis with respiratory arrest (Refs. 1, 4, 6, 9, and 15). Neomycin sulfate is recognized as having an undesirable sensitization potential (i.e., allergic response) (Refs. 1, 9, 12, and 17). Moreover, cross-sensitization to structurally related aminoglycosides may occur (Refs. 1, 6, 11, 12, and 17). The agency is particularly concerned about the risk of cross-sensitization because it may preclude future therapy with other potentially lifesaving aminoglycoside antibiotics (Refs. 9 and 12). In this regard, the agency has received a number of adverse reaction reports telling of hypersensitivity reaction to neomycin sulfate.

Some of the adverse reaction reports show that the sterile powder certified by FDA only for intramuscular use (i.e., as an injectable) in the treatment of urinary tract infections is being used to prepare irrigation solutions. As indicated above, the use of neomycin sulfate in the irrigation of wounds has been found to be without substantial evidence of effectiveness. Moreover, there is no evidence to provide safe concentrations and safe dosage limits for this use, and there is evidence that significant amounts of neomycin sulfate are absorbed systemically following its use in an irrigant solution during surgery, amounts that are comparable to amounts absorbed from an intramuscular injection site (Refs. 9, 12, 13, and 16). Use of neomycin sulfate as an irrigant may thus cause the same toxic effects as are produced by intramuscular administration (Refs. 4, 6, 9, 14, and 16). With respect to this use, the agency has received reports of total or partial deafness, ear disorders, kidney failure, heart arrest, paralysis, and coma.

Based on this evidence, FDA's Anti-Infective Agents Advisory Committee was requested to consider the advisability of allowing the continued marketing of sterile neomycin sulfate for parenteral use. At a meeting on April 4, 1977, the Committee concluded that the risk/benefit ratio for parenteral neomycin sulfate did not warrant its continued marketing and recommended that the dosage form no longer be certified. The Committee expressed its concern about unapproved uses of neomycin sulfate, including its use as an irrigant. Additionally, the Committee stated that in its opinion there is essentially no known use of this dosage form in the practice of medicine for the single remaining approved indication, treatment of urinary tract infection. (Many authors (Refs. 6, 8, and 17) agree with this opinion.)

In its consideration of this issue, the Committee noted that newer, safer antibiotics, as effective as parenteral neomycin sulfate, are avilable and have been widely accepted and that, therefore, neomycin sulfate is no longer an appropriate treatment for this indication.

Copies of the minutes of the Anti-Infective Agents Advisory Committee meeting are available for public inspection at the office of the Hearing Clerk (address above) between 9 a.m. and 4 p.m., Monday through Friday.

The agency has evaluated all available data and tentatively concludes that the risks involved in the use of parenteral neomycin sulfate outweigh any benefits that might be derived from such use, and that provisions for its certification, therefore, should be revoked.

FDA proposes to make this revocation effective 60 days after date of publication of the final rule in the Federal Register. If this proposal to revoke certification of sterile neomycin sulfate is finalized, all outstanding certificates for batches of sterile neomycin sulfate packaged for parenteral use will be revoked on the date the regulation is effective. The agency also proposes to require a recall to the retail level for all products covered by these certificates. In the event of a recall, holders of the certificates will be notified by letter of the revocations and of the details of the recall request.

Other dosage forms of neomycin sulfate (oral, dermatologic, ophthalmic, and otic) and sterile and nonsterile bulk neomycin sulfate used in the preparation of some of these dosage forms will not be affected by this action.

The agency has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and, therefore, consideration by the agency of the need for preparing an

environmental impact statement is not required.

References

The following material is on public file in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, where it may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

(1) Lechevalier, H. F., "The 25 Years of Neomycin," *CRC Critical Reviews in Microbiology*, pp. 359-397, 1975.

(2) Jawetz, E., "Polymyxin, Neomycin, Bacitracin" *in* "Antibiotics Monograph No. 5," Edited by Welch, H. and F. Marti-Ibanez, Medical Encyclopedia, Inc., New York, p. 40, 1956.

(3) Lowry, L. L., M. May, and P. Pastore, "Acute Histopathologic Inner Ear Changes in Deafness Due to Neomycin: A Case Report," *Annals of Otology, Rhinology and Laryngology*, 82:876-880, 1973.

(4) Masur, H., P. K. Whelton, and A. Whelton, "Neomycin Toxicity Revisited," *Archives of Surgery*, 111:822-825, 1976.

(5) Noone, P., "Use of Antibiotics: Aminoglycosides," *British Medical Journal*, 2(6136): 549-552, 1978.

(6) Weinstein, L., "Antimicrobial Agents: Streptomycin, Gentamicin, and Other Aminoglycosides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Company, New York, pp. 1178-1180, 1975.

(7) American Medical Association Department of Drugs, Chapter 52, "Aminoglycosides" *in* "American Medical Association Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 765-766, 1977.

(8) Hoeprich, P. D., "Antimicrobics and Anthelmintics for Systemic Therapy," *in* "Infectious Diseases," 2d Ed., Edited by Hoeprich, P. D., Harper & Row, Hagerstown, MD, pp. 172-173, 1977.

(9) The Medical Letter, Inc., "Topical Neomycin," *The Medical Letter*, Vol. 15, No. 25, 1973.

(10) Nachamie, B. A., R. S. Siffert, and M. S. Bryer, "A Study of Neomycin Instillation Into Orthopedic Surgical Wounds," *Journal of the American Medical Association*, 204:687-689, 1968.

(11) Schorr, W. F., F. J. Wenzel, and S. I. Hegedus, "Cross-Sensitivity and Aminoglycoside Antibiotics," *Archives of Dermatology*, 197:533-539, 1973.

(12) Anderson, M. D., "Neomycin Ototoxicity Associated with Wound Irrigation in the Local Treatment of Osteomyelitis," *Journal of Florida Medical Association*, 65:20-21, 1978.

(13) Weinstein, A. J., M. C. McHenry, and T. L. Gavan, "Systemic Absorption of Neomycin Irrigating Solutions," *Journal of the American Medical Association*, 238:152-153, 1977.

(14) Myerson, M., H. F. Knight, A. J. Gambarini, and T. L. Curan, "Intrapleural Neomycin Causing Ototoxicity," *The Annals of Thoracic Surgery*, 9:483-486, 1970.

(15) Kelly, P. J., W. J. Martin, and M. B. Coventry, "Chronic Osteomyelitis 11 Treatment with Closed Irrigation and Suction," *Journal of the American Medical Association*, 213:1843-1848, 1970.

(16) Gruhl, V. R., "Renal Failure, Deafness, and Brain Lesions Following Irrigation of the Mediastinum with Neomycin," *Annals of Thoracic Surgery*, 11:376-379, 1971.

(17) Gardner, S., "Over-the-Counter Drugs," Federal Register, 42 FR 17660-17667, April 1, 1977.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 444 be amended in § 444.42a by revising paragraph (a)(2) and (3), deleting paragraph (a)(4), and revising paragraph (b)(1)(i) (*d*) and (ii) to read as follows:

§ 444.42a Sterile neomycin sulfate.

* * * * *

(a) * * *

(2) *Labeling.* It is to be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Request for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, toxicity, moisture, pH, and identity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

* * * * *

(b) * * *

(1) * * *

(i) * * *

(d) Preparation of sample. Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with sufficient solution 3 to obtain a reference concentration of 1.0 microgram of neomycin per milliliter (estimated).

* * * * * *

(ii) *Plate assay using Staphylococcus aureus (ATCC 6538P).*[1] Proceed as directed in paragraph (b)(1)(i) of this section, except that the reference concentration of the sample under test is 10.0 micrograms of neomycin per milliliter; the concentrations of the standard curve solutions are 6.4, 8.0, 10.0, 12.5, 15.6 micrograms of neomycin per milliliter; and the suspension of the test organism, *Staphylococcus aureus* (ATCC 6538P),[1] is adjusted so that a 1:19 dilution will give 25 percent light transmission and the usual inoculum for each 100 milliliters of agar for the seed layer is 0.2 milliliter of diluted suspension.

* * * * *

Interested persons may, on or before September 25, 1979 submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments. The comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Interested persons may also, on or before August 27, 1979 submit to the Hearing Clerk (address above) a request for an informal conference. The participants in an informal conference, if one is held, will have until September 25, 1979 or 15 days from the day of the conference, whichever is later, to submit their comments.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 17, 1979.

J. Richard Crout,

Director, Bureau of Drugs.

[FR Doc. 79-22890 Filed 7-26-79; 8:45 am]

BILLING CODE 4110-03-M

[1] Available from: American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852.

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Secretary

[24 CFR Part 203]

[Docket No. R-79-695]

Sales of Insured Mortgage or Loan to Approved Mortgagee or Lender

AGENCY: Department of Housing and Urban Development.

ACTION: Notice of Transmittal of Proposed Rule to Congress under

APPENDIX 6:

recognized as safe (GRAS) status of ammoniated glycyrrhizin as a direct human food ingredient with specific limitations. This action is taken in response to two requests for extension of the comment period.

DATE: Written comments by October 15, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Foods (HFF–335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, DC 20204, 202–472–4750.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 15, 1979 (44 FR 28334), the Food and Drug Administration (FDA) amended its proposal to affirm the GRAS status of ammoniated glycyrrhizin as a direct human food ingredient with specific limitations. Interested persons were invited to submit comments on the amended proposal by July 16, 1979.

On June 15, 1979, a letter was received from the Henry H. Ottens Manufacturing Co., Inc. The firm requested a 90-day extension of the comment period for the amended GRAS affirmation proposal for ammoniated glycyrrhizin to allow sufficient time to prepare comments on the proposed rule.

Additionally, a second request was received on June 26, 1979 from Burditt and Calkins for a 6-month extension of the comment period for the amended proposal.

The agency regards the opportunity to comment on GRAS affirmation proposals as an important part of the GRAS review process. An extension of the comment period for this proposal would be appropriate. However, a 6-month extension of the comment period would unduly delay the rulemaking proceedings. The agency has considered both requests and has determined that an extension of the comment period for 90 days would provide ample time for all interested parties to prepare and submit comments to the May 15, 1979, amended proposal.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), the comment period for the amended GRAS affirmation proposal for ammoniated glycirrhizin is extended an additional 90 days.

Accordingly, interested persons may, on or before October 15, 1979, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 465, 5600 Fishers Lane, Rockville, MD 20857, written comments (preferably four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding the proposal. The envelope containing the comments should be prominently marked "Ammoniated Glycyrrhizin." Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: July 20, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 79–23130 Filed 7–24–79; 10:18 am]

BILLING CODE 4110–03–M

Food and Drug Administration

[21 CFR Parts 201, 207, and 314]

[Docket No. 78N–0320]

Requirements for Designating the Manufacturer's Name on a Drug or Drug Product Label; Reopening of Comment Period and Availability of Department of Justice Analysis of Economic Effects of Proposal

Correction

In FR Doc. 79–19722 appearing at page 37234 in the issue for June 26, 1979, make the following corrections:

(1) On page 37235, in the middle column, in the 6th line from the top of the page, substitute the word "if" for the word "is".

(2) On page 37236, in the first column, in the 27th line from the top of the page, substitute the word "of" for the word "or".

BILLING CODE 1505–01–M

[21 CFR Part 444]

[Docket No. 79N–0155]

Neomycin Sulfate for Prescription Compounding; Proposed Revocation of Certification

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) proposes to amend the antibiotic drug regulations by revoking provisions for certification of nonsterile neomycin sulfate for prescription compounding. This action is being taken because the risks of the drug outweigh the drug's benefits. This proposal, when final, would remove the drug from the market.

DATE: Comments by September 25, 1979; requests for an informal conference by August 27, 1979. FDA proposes that the final rule based on this proposal effective 60 days after its date of publication in the **Federal Register.**

ADDRESS: Written comments or requests for an informal conference to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Merle L. Givson, Bureau of Drugs (HFD–140), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4310.

SUPPLEMENTARY INFORMATION: This proposed rule would revoke the provisions of the antibiotic drug regulations that provide for certification of nonsterile neomycin sulfate for prescription compounding. This action is being taken because (1) the drug is being used for indications for which it lacks evidence of effectiveness and for which there is clinical evidence of significant risk to the patient and (2) the drug is no longer necessary for the use for which it was initially made available—as a dermatologic preparation—because neomycin sulfate is available from manufacturers in prepared forms for dermatologic use.

Neomycin sulfate was first approved for marketing on March 7, 1951 and became subject to batch certification on May 1, 1963. A regulation published in the **Federal Register** of March 21, 1964 (29 FR 3622) provided for the certification of nonsterile neomycin sulfate for prescription compounding. The regulation was intended to make available to pharmacists bulk neomycin sulfate for the extemporaneous preparation of drugs for dermatologic use. Because the drug was shipped in bulk for pharmacy compounding, it was permitted to be shipped without full disclosure labeling, i.e., a package insert. As a consequence, its labeling did not identify the drug's approved indications for use and did not give much of the other information, such as adverse reactions or warnings, commonly found in prescription drug labeling.

As part of the Drug Efficacy Study Implementation (DESI), the agency published its findings in the **Federal Register** of May 13, 1970 and February 29, 1972 (35 FR 7464 and 37 FR 4224) regarding the National Academy of Science/National Research Council (NAS/NRC) review of the efficacy of certain neomycin sulfate preparations

for their labeled indications. Nonsterile neomycin sulfate for prescription compounding was not reviewed because, as noted, its labeling did not identify its indications for use. Among other findings, the 1972 DESI notice announced that sterile neomycin sulfate powder lacked substantial evidence of effectiveness for a variety of uses including (1) its use in wet dressings, packs, and irrigations to treat secondarily infected wounds and ulcers, and (2) its use for intestinal instillation in emergency abdominal surgery.

As a result of the DESI review, 5- and 10-gram (g) packages of sterile neomycin sulfate were no longer certified and only a small vial size, 0.35 g neomycin per vial, was left on the market. A proposal to revoke certification of sterile neomycin sulfate powder, published elsewhere in this issue of the **Federal Register**, discusses in more detail the 1970 and 1972 DESI announcements.

Information that the agency has reviewed over the past few years from several sources shows that because the larger packages of sterile neomycin sulfate powder are no longer available, nonsterile neomycin sulfate for prescription compounding is being sterilized or otherwise processed for use in irrigation solutions and for other uses in the treatment of conditions for which the drug lacks evidence of effectiveness. Information that the agency has received from drug manufacturers of neomycin sulfate for prescription compounding, as well as information in the published literature, strongly suggests that the drug is being used to prepare solutions that are then sterilized and used for intraperitoneal irrigations, intrapleural irrigations, and irrigations of other surgical wounds. For example, one manufacturer has informed the agency of its "relative certainty" that the nonsterile powder for prescription compounding is being sterilized and used for a variety of purposes. The company asked that the regulation providing for certification of the product be amended to require warnings regarding the possible risks of drug use. The company has also informed FDA that it has received more than 100 written inquires concerning the sterilization, stability, and use for topical irrigation of neomycin sulfate solutions, which were presumably to be compounded from the bulk nonsterile drug.

The scientific literature also supports a conclusion that nonsterile neomycin sulfate is being widely misused. An article in *Hospital Pharmacy* (Vol. 7, No. 5, 1972, pp. 146–149) refers to the discontinuation of larger sizes of sterile neomycin and describes procedures for preparing a sterile solution from available nonsterile neomycin sulfate. The article suggests several uses for such a preparation, including its use as a wet dressing for extensive burns, in irrigation of wounds, and in intraperitoneal instillation. Copies of the manufacturer's letter to FDA and the article from *Hospital Pharmacy* have been placed on file in the office of the Hearing Clerk, FDA (address above).

The certification statistics for nonsterile neomycin sulfate for prescription compounding also show that significant amounts of the drug are now being used for indications lacking substantial evidence of effectiveness. The amounts of the drug certified for all manufacturers for the years 1969 through 1977 are as follows:

Year	Amount (kg)
1969	1,307.9
1970	1,619.2
1971	1,652.2
1972	3,231.8
1973	2,629.9
1974	3,094.7
1975	3,382.2
1976	3,643.6
1977	2,180.7

These figures show a dramatic increase in the amount of nonsterile neomycin sulfate for prescription compounding certified after the publication of the February 29, 1972 DESI notice that, in effect, significantly reduced the availability of sterile neomycin sulfate.

Thus, the unavailability of large packages of sterile neomycin sulfate has apparently resulted in significant quantities of nonsterile neomycin sulfate for prescription compounding being used for indications lacking evidence of effectiveness. Such uses are not only without benefit, but they expose the patient to the risk of serious toxic effects, including ototoxicity (hearing loss) and nephrotoxicity (kidney damage). There have been a growing number of reports in the literature of serious adverse reactions to the use in irrigation solutions of neomycin sulfate solutions. There is evidence that significant amounts of the drug are absorbed systemically following its use in irrigation solution, amounts comparable to amounts absorbed when the drug is taken systemically. As a consequence, use of neomycin sulfate as an irrigant may produce the same toxic effects as are produced by the drug's systemic use.

In view of this data showing significant use of neomycin sulfate for prescription compounding for indications for which the drug not only lacks substantial evidence of effectiveness but also poses risks for the patient, the agency asked the Anti-Infective Agents Advisory Committee to consider the problems associated with the continued certification of this product. At its meeting on April 4 and 5, 1977, the Committee recommended the immediate inclusion on the labeling for this product of a boxed warning emphasizing the drug's ototoxicity and nephrotoxicity. Additionally, the Committee recommended that the agency take steps to end the marketing of the product if, after a period of time to be determined by the agency, manufacturers failed to submit adequate data to establish the safety and efficacy of the drug for specific indications. Copies of the minutes of the Committee meeting are available for public inspection at the office of the Hearing Clerk, address given above, between 9 a.m. and 4 p.m., Monday through Friday.

FDA has evaluated the Advisory Committee's recommendation and all other available data and tentatively concludes that it is in the best interest of the public no longer to accept neomycin sulfate for prescription compounding for certification. Because sufficient data to ensure adequately the safe and effective use of neomycin sulfate for prescription compounding currently do not exist, the agency does not believe that the continued marketing of the drug pending the submission of further data, as recommended by the Advisory Committee, is justified. The primary purpose in certifying this drug—to make available a bulk product for the compounding of neomycin sulfate dermatologics—is now served by the availability of a variety of commercially prepared dermatologic drug products. Because the current misuse of this product creates an unfavorable benefit-to-risk ratio and because neomycin sulfate is available from manufacturers in prepared form for dermatologic use, the continued certification of nonsterile neomycin sulfate for prescription compounding should be discontinued.

FDA proposes to make this revocation effective 60 days after date of publication of a final rule in the **Federal Register**. If the proposal is finalized, all outstanding certificates for batches of neomycin sulfate for prescription compounding will be revoked on the date that revision of the regulation is effective. The agency also proposes to request a recall to the retail level for all products covered by these certificates. If a recall takes place, holders of the certificates will be notified by letter of

the revocations and of the details of the recall request.

Neomycin sulfate for prescription compounding is only one of several neomycin sulfate preparations made available through the certification process. Other preparations, including otic, ophthalmic, oral, and dermatologic dosage forms, continue to be regularly certified and marketed and are not affected by this proposal.

The agency has determined that this document does not contain an agency action covered by § 25.1(b) (21 CFR 25.1(b)) and, therefore, consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 444 be amended by revoking and reserving § 444.942a *Neomycin sulfate for prescription compounding.*

Interested persons may, on or before September 25, 1979, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Interested persons may, also, on or before August 27, 1979, submit to the Hearing Clerk (address above) a request for an informal conference. The participants in an informal conference, if one is held, will have until August 27, 1979, or 15 days from the day of the conference, whichever is later, to submit their comments.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 17, 1979.

J. Richard Crout,

Director, Bureau of Drugs.

[FR Doc. 79–22889 Filed 7–26–79; 8:45 am]

BILLING CODE 4110–03–M

[21 CFR Part 444]

[Docket No. 79N–0151]

Certification of Sterile Neomycin Sulfate for Parenteral Use; Proposed Revocation of Provisions

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration proposes to amend the antibiotic regulations to revoke provisions for certification of neomycin sulfate in sterile vials for parenteral use. This action is being taken on the basis of widespread evidence that the drug's risks outweigh its benefit. This action would remove these drug products from the market.

DATES: Comments by September 25, 1979; requests for informal conference by August 27, 1979. FDA proposes that the final regulation based on this proposal become effective 60 days after the date of its publication in the **Federal Register.**

ADDRESS: Written comments or requests for an informal conference to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Merle Gibson, Bureau of Drugs (HFD–140), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4310.

SUPPLEMENTARY INFORMATION: FDA is proposing to revoke the regulation providing for certification of sterile neomycin sulfate for parenteral use.

Neomycin sulfate was discovered in 1949 when Waksman and Lechevalier isolated a soil organism, *Streptomyces fradiae,* which produced a new antibiotic containing a group of antibacterial substances. When purified, it was found to be a complex of three compounds, neomycins A, B, and C. Each compound demonstrated its own antibacterial activity. Commercial neomycin preparations consist primarily of neomycin B.

Before 1970, the approved labeling of neomycin sulfate indicated the drug for a number of uses, including:

(1)Intramuscular use (as an injectable) in certain serious systemic infections and urinary tract infections;

(2) Intraperitoneal instillation in treating peritonitis and preventing peritonitis following peritoneal contamination during surgery;

(3) Topical use in dressings, packs, and irrigations; and

(4) Intestinal instillation in emergency abdominal surgery.

The pre-1970 labeling for neomycin sulfate warned of the drug's potential ototoxicity (predominantly auditory toxicity or hearing loss) and nephrotoxicity (kidney damage).

On May 13, 1970 (35 FR 7464) and Februrary 29, 1972 (37 FR 4224), notices pertaining to neomycin sulfate sterile powder were published in the **Federal Register** as a result of the Drug Efficacy Study Implementation (DESI 7837).

The May 1970 notice announced FDA's conclusions regarding certain preparations of neomycin sulfate sterile powder reviewed by the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group and provided an opportunity for comment and for submission of pertinent data to support the indications.

The February 1972 notice amended the earlier notice as a result of a reevaluation of the antibiotic drug preparations involved. The 1970 notice as amended by the 1972 notice included findings that:

1. Neomycin sulfate sterile powder is effective for intramuscular use in the treatment of urinary tract infections due to susceptible strains of certain organisms *(Psuedomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli,* and *Enterobacter aerogenes).*

2. The drug lacks substantial evidence of effectiveness for all other labeling claims. These include: treatment of peritonitis (intraperitoneal instillation) and prevention of peritonitis following peritoneal contamination during surgery; for use as wet dressings, packs, or irrigations in secondarily infected wounds and ulcers, varicose ulcers, and infections of the eye; and for intestinal instillation in emergency abdominal surgery.

3. Labeling for the remaining marketed preparations should include a "Box Warning" and statements in the "Precautions" and "Adverse Reactions" sections emphasizing the potential nephrotoxic and ototoxic effects of neomycin sulfate and its potential for causing respiratory paralysis from neuromuscular blockade.

4. Previously marketed package sizes of 5 and 10 grams of sterile powder are inappropriate for preparation of solutions for intramuscular

APPENDIX 7:

or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request the hearing, making findings and conclusions and denying a hearing.

All submissions under this order are to be filed in three copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 444

Antibiotics.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 444 is amended as follows:

PART 44—OLIGOSACCHARIDE ANTIBIOTIC DRUGS

1. The authority citation for 21 CFR Part 444 continues to read as follows:

Authority: Sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357); 21 CFR 5.10.

2. Section 444.942a is amended by revising the section heading and by revising paragraphs (a)(1) introductory text, (3) introductory text, and (4)(i), to read as follows:

§ 444.942a Neomycin sulfate for compounding oral products.

(a) * * *

(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate for compounding oral products is the sulfate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

* * * * *

(3) *Labeling.* It shall be labeled in accordance with the requirements prescribed by § 432.5(a) of this chapter. Its expiration date is 12 months.

(4) * * *

(i) In addition to complying with the conditions of § 431.1 of this chapter, a person who requests certification of a batch of neomycin sulfate for compounding oral products shall submit with the request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by results of tests and assays made on the batch for potency, moisture, pH, and identity.

* * * * *

Dated: March 30, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88-8189 Filed 4-14-88; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 444

[Docket No. 79N-0151]

Oligosaccharide Antibiotic Drugs; Sterile Neomycin Sulfate

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the antibiotic drug regulations to revoke the provisions for certification of neomycin sulfate in sterile vials for parenteral use. This action is being taken because the risks involved in the parenteral use of neomycin sulfate are judged to outweigh any benefits that might be derived from its continued availability. FDA is offering an opportunity for a hearing on objections to this revocation under the formal rulemaking provisions in section 507(f) of the Federal Food, Drug, and Cosmetic Act (the act) and the Administrative Procedure Act (5 U.S.C. 556 and 557). Elsewhere in this issue of the **Federal Register** is a notice offering an opportunity for a hearing on the proposal to withdraw the approval of antibiotic applications and abbreviated antibiotic applications for neomycin sulfate in sterile vials for parenteral use.

DATES: Effective June 14, 1988; comments, notices of participation, and requests for hearing by May 16, 1988; data, information, and analyses to justify a hearing by June 14, 1988.

ADDRESSES: Written comments concerning requests for hearing, supporting data, and information to Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this final rule to a specific product to Division of Drug Labeling Compliance (HFN-310), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judy O'Neal, Center for Drug Evaluation and Research (HFN-366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8041.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 27, 1979 (44 FR 44180), FDA proposed to revoke the provisions of its antibiotic drug regulations (21 CFR 444.42a) that provide for the certification of neomycin sulfate in sterile vials for parenteral use. This action was taken because there is clinical evidence that parenterally administered neomycin sulfate can induce significant toxicity including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade. In addition, there is evidence that the sterile vial of neomycin sulfate, which has been approved by FDA only for intramuscular administration in the treatment of certain urinary tract infections, is being used to prepare irrigation solutions. As concluded in the Drug Efficacy Study Implementation notice published on February 29, 1972 (37 FR 4224), evidence of effectiveness is lacking for the use of sterile neomycin sulfate in the irrigation of wounds. Moreover, there is clinical evidence that such use poses a significant risk to the patient, as described in the July 27, 1979, proposal and in another final rule published elsewhere in this issue of the **Federal Register** concerning neomycin sulfate for prescription compounding. A third reason for the proposed action was that, as concluded by FDA's Anti-Infective Agents Advisory Committee, use of this dosage form for the single remaining approved indication, the treatment of urinary tract infection, is no longer acceptable because of the availability of newer, safer antibiotics that are as effective as, or more effective than, parenteral neomycin sulfate and that do not present comparable risks.

After the proposal regarding sterile neomycin sulfate was published on July 27, 1979, FDA received three requests for an informal conference, and also received two requests for an extension of the comment period on the related proposal regarding nonsterile neomycin sulfate for prescription compounding. A notice of opportunity for an informal conference was published in the **Federal Register** of October 19, 1979 (44 FR 60331), and an informal conference was held on November 20, 1979. In addition, the comment period was extended for 30 days after the date of the informal conference.

The agency has carefully considered all of the comments received on the proposal and has concluded that the risks involved in the parenteral use of neomycin sulfate outweigh any benefits that might be derived from such use. This final rule amends the regulations to

revoke provisions for certifying neomycin sulfate in sterile vials for parenteral use. In a notice published elsewhere in this issue of the **Federal Register**, FDA is proposing to withdraw approval under section 505(e) of the act of the antibiotic applications and abbreviated antibiotic applications for sterile neomycin sulfate.

Only neomycin sulfate in sterile vials for parenteral use is affected by this action. Other dosage forms of neomycin sulfate (oral, dermatologic, ophthalmic, and otic) and sterile and nonsterile bulk neomycin sulfate used in the preparation of some of these dosage forms are not affected by these actions. However, elsewhere in this issue of the **Federal Register**, FDA is publishing a final rule amending the antibiotic drug regulations (21 CFR 444.942a) for nonsterile neomycin sulfate for prescription compounding. That amendment changes the product name from "Neomycin sulfate for prescription compounding" to "Neomycin sulfate for compounding oral products" and requires package insert labeling that includes indications for use and warnings about the drug's toxicity.

II. Responses to the Comments

In addition to the comments submitted during the informal conference, the agency received eight written comments. Four of the written comments opposed the proposal. A summary of the substantive comments and the agency's responses follow:

1. Several comments said that sterile neomycin sulfate powder in vials is used to prepare irrigation solutions. The comments said that the solution is used in augmentation mammaplasty, as a wash for other silastic implants for total joint replacement procedures, and as a neurosurgical irrigation solution. The comments also said that sterile neomycin sulfate powder in vials is used to prepare neomycin enema and neomycin colostomy irrigations and is used in the preoperative preparation of surgical patients. One comment noted that the injectable form is more convenient because it does not require subsequent sterilization. The comment also said that the solution is effective since wound infections have not been observed after its use. Another comment explained in detail that the contents of the sterile vial are added to saline or water to make irrigating solutions. The comment contended that the sterile vial provides a quick method for getting a 2-percent or less solution when there is fecal spillage in the abdominal cavity. The comment noted the use of a sterile 5-percent irrigating solution in infected hernia wounds. The comment also claimed that if the drug is no longer permitted for topical application, the surgeon will be unable to manage surgical complications. Several comments stated that orthopedic surgeons and other surgeons continue to use neomycin in wound irrigations that require a substantial number of sterile 500-milligram (mg) vials (containing 350 mg of neomycin base). One physician argued that both the nonsterile powder and the sterile neomycin sulfate powder in vials have been used for 13 years to prepare topical sprays, gels, and ointments for patients undergoing cancer chemotherapy in protected environment units. The comment said that topical formulations containing neomycin and other antibiotics in combination are applied to the gums, ears, groin, perianal region, rectum, vagina, anterior nares, or throat up to four times a day.

The agency advises, as explained in the proposal of July 27, 1979 (44 FR 44181), to this final rule and in greater detail in the final rule about nonsterile neomycin sulfate for prescription compounding, published elsewhere in this issue of the **Federal Register**, that the use of neomycin sulfate for irrigation lacks evidence of effectiveness and has produced clinical evidence of significant risk to the patient. Since 1972 sterile neomycin sulfate powder in vials has been approved by FDA only for intramuscular use in the treatment of certain urinary tract infections. In addition, because of the drug's toxicity, its labeling has stated that the drug should be reserved for hospitalized cases with this condition in which no other antimicrobial agent is effective. Many other less toxic and more effective aminoglycosides (such as gentamicin, tobramycin, netilmicin, and amikacin) and other antimicrobial agents are available as alternatives for the approved indication recommended in the labeling.

2. Several comments said that, with respect to both sterile and nonsterile formulations, prudent neomycin sulfate therapy has a place in the physician's armamentarium of antibiotics. One comment said that toxic effects are always considered by health professionals when drug therapy is designed, and that risks and benefits must be weighed against each other when prescribing any drug.

Although the agency agrees that risks and benefits of any drug therapy must be weighed against each other, toxicity associated with parenteral administration of neomycin sulfate is well documented and more severe than that associated with available alternatives. Most experts have avoided the parenteral use of neomycin sulfate since the end of the 1950's because of its toxicity and because of the availability of safer drugs. FDA's Anti-Infective Drugs Advisory Committee recommended that the preparation be removed from the market.

3. One comment contended that there are very limited, unique uses for sterile neomycin sulfate, and that appropriate labeling can control any misuse of the product.

The agency does not believe that labeling would effectively control the misuse of sterile neomycin sulfate nor that unique uses of neomycin sulfate remain. Such labeling is justified only when it can be demonstrated that the continued use of the drug product will serve a useful purpose provided the labeling is observed. As already explained in this document and in the proposal, sterile neomycin sulfate is approved only for intramuscular administration in the treatment of certain urinary tract infections for hospitalized patients for whom no other antimicrobial agent is effective. Despite these restrictions in the product's labeling, this product continues to be used for irrigation in the treatment of various other conditions with significant risk to patients. In addition, FDA's Anti-Infective Drugs Advisory Committee concluded in 1977 that this dosage form is essentially no longer used for the single remaining approved indication, the treatment of certain urinary tract infections. The committee also noted that newer, safer antibiotics, as effective as parenteral neomycin sulfate, are available for this indication.

4. One comment took issue with the statement in the proposal that FDA will "require a recall to the retail level for all products covered by these certificates." The comment argued that section 301(k) of the Federal Food, Drug, and Cosmetic Act, which prohibits the doing of any act that would result in the adulteration or misbranding of an article being held for sale after shipment in interstate commerce, would not be applicable to the revocation of a certificate by FDA.

This product is currently exempt from certification under the provisions of § 433.1 (21 CFR 433.1). Therefore, the issue of the revocation of certification is now moot. In view of the time that has passed since the proposed rule was published, FDA will not request that manufacturers initiate a recall. However, when the final rule is effective, batches of sterile neomycin sulfate packaged in 0.35-gram vials will no longer be certified or released, nor will the product be exempt from

certification except where subject to an approved application. With the withdrawal of approval of the applications, the product may not be legally shipped in interstate commerce.

III. Amendments to the Antibiotic Drug Regulations

Under 21 CFR Part 433.1 (a) and (b), antibiotic drugs are exempt from batch certification requirements if (1) the drug is approved for marketing under an appropriate antibiotic application or abbreviated antibiotic application, (2) the drug is packaged and labeled for dispensing in accordance with the applicable regulation or approved application, (3) the bulk drug used in preparing the antibiotic drug product meets the standards of identity, strength, quality, and purity specified in the applicable regulation or approved application, and (4) the antibiotic drug product meets the standards of identity, strength, quality, and purity specified in the applicable regulation or approved application.

The regulation applicable to sterile neomycin sulfate for parenteral use, § 444.42a, is being amended to delete (1) the provision in paragraph (a)(2) for the 0.35-gram package for dispensing, (2) the provision in paragraph (a)(3) for labeling of the drug packaged for dispensing, (3) the provision in paragraph (a)(4) describing samples required for certification of a batch packaged for dispensing, and (4) provisions under paragraphs (b)(1)(i)(*d*) and (b)(1)(ii) describing potency testing of the drug packaged for dispensing. With the deletion of these provisions, neomycin sulfate packaged in sterile vials for dispensing can neither be certified nor released. Except where other labeling and standards of identity, strength, quality, and purity have been approved in an applicable application, the product is not exempt from batch certification requirements.

As stated in the proposal (44 FR 44181), the revocation becomes effective 60 days after the date of publication of this final rule. At that time, batches of sterile neomycin sulfate packaged in 0.35-gram vials will no longer be certified, released, or exempt from certification, except for those products covered by approved antibiotic applications. Shipment in interstate commerce of sterile neomycin sulfate packaged for parenteral use that is not certified, released, or exempt from certification will be unlawful.

IV. Economic and Environmental Impact

The agency has determined under 21 CFR 25.24(c)(3) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This final rule does not require a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12291 does not apply to actions, such as this, at the stage where they are subject to opportunity for hearing under 5 U.S.C. 556 and 557. Furthermore, the Regulatory Flexibility Act does not apply to this proceeding because the proposed rule was issued before the effective date of that Act. Nevertheless, the agency has examined the economic impact of this final rule and has determined that this impact is insignificant. Because the product is not currently being marketed by any manufacturer, FDA believes no additional burdens are imposed. Therefore, the agency concludes that this final rule does not meet the criteria for a major rule as defined in Executive Order 12291, and that this final rule will not have a significant economic impact on small entities as defined by the Regulatory Flexibility Act.

V. Notice of Opportunity for a Hearing

Any person who will be adversely affected by the final rule amending the antibiotic regulations may file objections to it and request a hearing as provided in section 507(f) of the act (21 U.S.C. 357). Reasonable grounds for the hearing must be shown, as specified in 21 CFR 314.300. If hearings are granted both on objections to the final rule and on the proposed withdrawal of approval of the applications that is published elsewhere in this issue of the **Federal Register**, the hearings will be combined in a single proceeding conducted under 5 U.S.C. 556 and 557 and 21 CFR Part 12. Any person subject to this final rule who decides to seek a hearing shall file: (1) On or before May 16, 1988, a written notice of participation and request for hearing, and (2) on or before June 14, 1988, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.300. Any other interested person may also submit comments. The procedures and requirements governing this notice of opportunity for hearing, a notice of participation and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in 21 CFR 314.300.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that no genuine and substantial issue of fact precludes the action taken by this order, or if a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request(s) the hearing, making findings and conclusions and denying a hearing.

All submissions under this order are to be filed in three copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 444

Antibiotics.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 444 is amended as follows:

PART 444—OLIGOSACCHARIDE ANTIBIOTIC DRUGS

1. The authority citation for Part 444 continues to read as follows:

Authority: Sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357); 21 CFR 5.10.

2. Section 444.42a is amended by removing paragraph (a)(2); by redesignating existing paragraphs (a) (3) and (4) as paragraphs (a) (2) and (3), respectively, and by revising redesignated paragraphs (a)(2) and (a)(3), and paragraphs (b)(1)(i)(d), and (b)(1)(ii) (removing the undesignated paragraph following (b)(1)(ii)), to read as follows:

§ 444.42a Sterile neomycin sulfate.

(a) * * *

(2) *Labeling.* It is to be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Request for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples required;

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams

(*b*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

* * * * *

(b) * * *

(1) * * *

(i) * * *

(*d*) *Preparation of sample.* Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with sufficient solution 3 to obtain a reference concentration of 1.0 microgram of neomycin per milliliter (estimated).

* * * * *

(ii) *Plate assay using Staphylococcus aureus (ATCC 6538P).*[1] Proceed as directed in paragraph (b)(1)(i) of this section, except that the reference concentration of the sample under test is 10.0 micrograms of neomycin per milliliter; the concentrations of the standard curve solutions are 6.4, 8.0, 10.0, 12.5, 15.6 micrograms of neomycin per milliliter; and the suspension of the test organism, staphylococcus aureus (ATCC 6538P),[1] is adjusted so that a 1:19 dilution will give 25 percent light transmission and the usual inoculum for each 100 milliliters of agar for the seed layer is 0.2 milliliter of diluted suspension.

* * * * *

Dated: March 30, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88-8192 Filed 4-14-88; 8:45 am]

BILLING CODE 4160-01-M

[1] Available from: American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852.

APPENDIX 8:

Dated: March 30, 1988

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88-8190 Filed 4-14-88; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 79N-0151]

Oligosaccharide Antibiotic Drugs; Sterile Neomycin Sulfate; Opportunity for Hearing on Proposal To Withdraw Approval of Applications

AGENCY: Food and Drug Administration.

ACTION: Notice of opportunity for hearing.

SUMMARY: The Food and Drug Administration (FDA) is offering an opportunity for a hearing on the proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for neomycin sulfate in sterile vials for parenteral use. This action is being taken because the risks involved in the parenteral use of neomycin sulfate are judged to outweigh any benefits that might be derived from its continued availability. FDA is offering an opportunity for a hearing on the proposal under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)).

DATES: Comments, notice of participation, and request for hearing by May 16, 1988; data, information, and analyses to justify a hearing by June 14, 1988.

ADDRESSES: Written comments concerning requests for hearing, supporting data, and information to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this notice to a specific product to Division of Drug Labeling Compliance (HFN-310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judy O'Neal, Center for Drug Evaluation and Research (HFN-366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8041.

SUPPLEMENTARY INFORMATION:

I. Background

In a final rule published elsewhere in this issue of the **Federal Register**, FDA is amending the antibiotic drug regulations to revoke the provisions for certification of neomycin sulfate in sterile vials for parenteral use. There is clinical evidence that parenterally administered neomycin sulfate can induce significant toxicity including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade. In addition, there is evidence that the sterile vial of neomycin sulfate, which has been approved by FDA only for intramuscular administration in the treatment of certain urinary tract infections, is being used to prepare irrigation solutions. As concluded by the Drug Efficacy Study Implementation notice published February 29, 1972 (37 FR 4224), evidence of effectiveness is lacking for the use of sterile neomycin sulfate in the irrigation of wounds. Moreover, there is clinical evidence that such use poses a significant risk to the patient, as described in the proposed rulemaking published July 27, 1979 (44 FR 44180), and in another final rule published elsewhere in this issue of the **Federal Register** concerning neomycin sulfate for prescription compounding. Another reason is that, as concluded by FDA's Anti-Infective Agents Advisory Committee, use of this dosage form for the single remaining approved indication, the treatment of urinary tract infection, is no longer acceptable because of the availability of newer, safer antibiotics that are as effective as, or more effective than, parenteral neomycin sulfate and that do not present comparable risks.

However, amending the antibiotic regulations, as proposed in the July 27, 1979, notice, is no longer sufficient to remove existing approved products from the market. In the **Federal Register** of September 7, 1982 (47 FR 39155), FDA amended the antibiotic drug regulations to exempt antibiotic-containing drugs from batch certification requirements. Under the new regulations specifying the conditions of the exemption (21 CFR 433.1(b)), an antibiotic drug product is exempt from batch certification requirements if it is packaged and labeled for dispensing in accordance with, and meets the standards of identity, strength, quality, and purity specified in, the applicable regulation except where other labeling and standards have been approved in an applicable antibiotic application or abbreviated antibiotic application. Therefore, in addition to revising the applicable regulations, it is necessary to withdraw approval of applications for the products. An antibiotic drug exempt from certification requirements under 21 CFR 433.1(b) is subject, following its approval, to section 505 of the act and applicable parts of the new drug regulations (21 CFR Parts 310 through 314 and 433.1(c)). This notice proposes to withdraw approval under section 505(e) of the act of the antibiotic applications and abbreviated antibiotic applications for sterile neomycin sulfate.

The following products, although no longer marketed, are known by FDA to be affected by this notice:

1. Neomycin Sulfate for Injection, U.S.P., covered by application number 60-366, E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540.

2. Mycifradin Injectable, covered by application number 60-477, The Upjohn Co., Kalamazoo, MI 49001.

3. Neomycin Sulfate for Injection, U.S.P., covered by application number 61-084, Pfizer, Inc., 235 East 42nd St., New York, NY 10017.

4. Neomycin Sulfate for Injection, U.S.P., covered by application number 61-198, Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.

On the basis of all the data and information available, the Director of the Center for Drug Evaluation and Research finds that neomycin sulfate in sterile vials is unsafe for parenteral use as provided for in its approved labeling.

Therefore, notice is given to the holders of the antibiotic applications listed above, and to all other interested persons, that the Director of the Center for Drug Evaluation and Research proposes to issue an order under section 505(e) of the act, withdrawing approval of the antibiotic applications and all amendments and supplements thereto, on the ground that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis for which the applications were approved.

In accordance with section 505 of the act and the regulations promulgated under it (21 CFR Parts 310 and 314), the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to the drug product named above (21 CFR 310.6) and not the subject of an antibiotic application are hereby given an opportunity for a hearing to show why approval of the application should not be withdrawn, and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug product named above and of all identical, related, or similar drug products not the subject of an approved application. If hearings are granted both on objections to the final rule published elsewhere in this issue of the **Federal Register** and on the proposed withdrawal of approval of the applications, the hearings will be combined in a single proceeding conducted under 21 CFR Part 12 and 5 U.S.C. 556 and 557.

In addition to the holders of the applications specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved antibiotic application, that is identical, related, or similar to the drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he or she manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he or she manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Division of Drug Labeling Compliance (address above).

This notice of opportunity for hearing on the proposed withdrawal of approval of the applications encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act (21 U.S.C. 321(p)), or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

The applicant or any other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file: (1) on or before May 16, 1988, a written notice of participation and request for hearing, and (2) on or before June 14, 1988, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments. The procedures and requirements governing this notice of opportunity for hearing, a notice of participation and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of participation and request for hearing, as required by 21 CFR 314.200, constitutes an election by the person not to make use of the opportunity for a hearing concerning the action and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and FDA will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that no genuine and substantial issue of fact precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request(s) the hearing, making findings and conclusions and denying a hearing.

All submissions under this notice are to be filed in three copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 507, 52 Stat. 1050–1053 as amended (21 U.S.C. 352, 355) and 59 Stat. 463 as amended (21 U.S.C. 357)) and under authority delegated to the Center for Drug Evaluation and Research (21 CFR 5.70, 5.78, and 5.82).

Dated: March 30, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88–8191 Filed 4–14–88; 8:45 am]

BILLING CODE 4160–01–M

APPENDIX 9:

FOR FURTHER INFORMATION CONTACT: Margaret F. Sharkey, Center for Drug Evaluation and Research (HFD–366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8041.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of April 15, 1988 (53 FR 12662), the Director of the Center for Drug Evaluation and Research offered an opportunity for a hearing on a proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for nonsterile neomycin sulfate for prescription compounding not labeled in accordance with applicable amended antibiotic regulations (21 CFR 444.942a). In the same issue (53 FR 12644), FDA amended the regulations governing these products and offered a labeling guideline because the drug was being used for indications for which it lacked evidence of safety and effectiveness, and for which there was clinical evidence of significant risk to the patient. The final rule became effective on June 14, 1988.

The amendments to 21 CFR 444.942a changed the product name from "neomycin sulfate for prescription compounding" to "neomycin sulfate for compounding oral products" and required product labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use.

Manufacturers and suppliers were notified that they would have to supplement their applications within 60 days of the effective date of the final rule to provide for the new product name and package insert labeling. Alternatively, a manufacturer or supplier could request a hearing. No supplements were submitted for any of the applications. One supplier, Pharma-Tek, Inc., requested a hearing.

The sponsors of the five products listed below failed to file a request for a hearing and did not supplement their applications. Accordingly, FDA is withdrawing approval of the following AADA's:

1. AADA 61–043; held by The Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
2. AADA 61–805; held by Pfizer, Inc., 235 East 42nd St., New York, NY 10017.
3. AADA 61–169; held by S.B. Penick and Co., 540 New York Ave., Lyndhurst, NJ 07071.
4. AADA 61–698; held by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.
5. AADA 62–385; held by Paddock Laboratories, Inc., 3101 Louisiana Ave. North, Minneapolis, MN 55421.

The Director of the Center for Drug Evaluation and Research, under the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052–1053 as amended (21 U.S.C. 355(e))) and under authority delegated to him (21 CFR 5.82), finds that clinical or other experience, tests, or other scientific data show that the drug products listed above are unsafe for use under the conditions of use upon basis for which their applications were approved. Therefore, pursuant to the foregoing finding, approval of the AADA's listed above is hereby withdrawn effective January 5, 1989. Shipment in interstate commerce of the products listed above will then be unlawful.

This notice does not apply to AADA 61–579, held by Pharma-Tek, Inc., P.O. Box AB, Huntington, NY 11743. The product covered by AADA 61–579 is the subject to a pending hearing request and will be the subject of a future **Federal Register** announcement.

Dated: November 28, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88–28027 Filed 12–5–88; 8:45 am]
BILLING CODE 4160–01–M

[Docket No. 79N–0151]

Oligosaccharide Antibiotic Drugs; Neomycin Sulfate for Injection; Withdrawal of Approval of Abbreviated Antibiotic Drug Applications

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of four abbreviated antibiotic drug applications (AADA's) for neomycin sulfate in sterile vials for injection. This withdrawal action is being taken because the risks involved in the parenteral use of neomycin sulfate are judged to outweigh any benefits that may be derived from its continued availability.

EFFECTIVE DATE: January 5, 1989.

FOR FURTHER INFORMATION CONTACT: Margaret F. Sharkey, Center for Drug Evaluation and Research (HFD–366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8041.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of April 15, 1988 (53 FR 12664), the Director of the Center for Drug Evaluation and Research offered an opportunity for a hearing on a proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for neomycin sulfate in sterile vials for parenteral use. FDA also amended the antibiotic regulations for sterile neomycin sulfate (21 CFR 444.42a) by deleting all provisions for the injectable dosage form so that neomycin sulfate packaged in sterile vials for dispensing could not be certified or released (see 53 FR 12658; April 15, 1988). These actions were deemed necessary because of the toxicity associated with the unapproved use of this drug in the irrigation of wounds. In addition, the Director concluded that the use of this dosage form for the single remaining approved indication, the treatment of urinary tract infection, is no longer acceptable because of the availability of newer, safer antibiotics that are as effective as, or more effective than, parenteral neomycin sulfate and that do not present comparable risks.

In response to the April 15, 1988, **Federal Register** notice, no holders of approved applications requested a hearing. Accordingly, FDA is withdrawing approval of the following applications:

1. AADA 60–366, Neomycin Sulfate for Injection, U.S.P., held by E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540.
2. AADA 60–477, Mycifradin Injectable, held by The Upjohn Co., Kalamazoo, MI 49001.
3. AADA 61–084, Neomycin Sulfate for Injection, held by Pfizer Inc., 235 East 42nd St., New York, NY 10017.
4. AADA 61–198, Neomycin Sulfate for Injection, U.S.P., held by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.

The Director of the Center for Drug Evaluation and Research, under the Federal Food, Drug and Cosmetic Act (sec. 505(e), 52 Stat. 1052–1053 as amended (21 U.S.C. 355(e))) and under authority delegated to him (21 CFR 5.82), finds that clinical or other experience, tests, or other scientific data show that the drug products listed above are unsafe for use under the conditions of use upon the basis for which their applications were approved. Therefore, pursuant to the foregoing finding, approval of the AADA's listed above is hereby withdrawn effective January 5, 1989. Shipment in the interstate commerce of the products listed above will then be unlawful.

Dated: November 28, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88-28028 Filed 12-5-88; 8:45 am]

BILLING CODE 4160-01-M

Health Care Financing Administration

[OACT-22-N]

Medicare Program; Employers and Duplicative Medicare Benefits

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice.

SUMMARY: This notice announces the national average actuarial value of additional Medicare Part A benefits available in 1989 as a result of the Medicare Catastrophic Coverage Act of 1988. Employers are required to examine the extent to which health benefits they provide to employees and retired former employees entitled to Medicare (including coverage for employees' and retired former employees' dependents entitled to Medicare) duplicate the new Part A and Part B benefits. If the duplicative benefits have a national average actuarial value of at least 50 percent of the value of the new Medicare benefits, the employer must offer a refund, additional benefits, or some combination thereof.

In computing the actuarial values of the duplicative benefits, employers have the option of using national average actuarial values we establish or calculating the actuarial value based on guidelines we establish. This notice contains both the national actuarial values we have determined and the guidelines for employers to use.

EFFECTIVE DATES: The provisions of this notice concerning Part A are effective January 1, 1989. The provisions of this notice concerning Part B are effective January 1, 1990.

FOR FURTHER INFORMATION CONTACT:

Kenneth Leong, (301) 966-7908, concerning the actuarial values and guidelines.

Herbert Pollock, (301) 966-4474, concerning all else.

SUPPLEMENTARY INFORMATION:

I. Background

The Medicare Catastrophic Coverage Act of 1988 (Pub. L. 100-360) was enacted on July 1, 1988. This act, which provides for benefits not previously available under Medicare, protects beneficiaries against costs associated with a catastrophic illness. The Act provides for expanded Part A benefits effective January 1, 1989 and expanded Part B benefits effective January 1, 1990.

Many beneficiaries have private health insurance coverage that supplements Medicare, usually through health benefits plans of current or past employers. Some of these health benefits plans offer protection against the costs of a catastrophic illness by limiting beneficiary out-of-pocket expenses or offering additional benefits, such as a longer period of hospitalization than Medicare covered; some plans may do both. In addition, some plans pay deductibles, coinsurances, the Part A premium where applicable, the Part B premium, or some combination of these benefits.

With the availability of expanded Medicare coverage beginning in 1989, beneficiaries that now are receiving additional benefits through their employers' health benefits plans would find that the coverages are duplicative and they reap little, if any, benefit from the Medicare catastrophic coverage changes. Therefore, Congress included section 421 in Pub. L. 100-360, which ensures that if an employer provided to employees or retired former employees,[1] as of July 1, 1988 (the date of enactment of Pub. L. 100-360) benefits that will be available to Medicare beneficiaries as a result of Pub. L. 100-360, the employer must offer additional benefits, a refund, or a combination thereof, if the duplicative benefits have an actuarial value of at least 50 percent of the national average actuarial value of the benefits added or increased by Pub. L. 100-360. Congress enacted technical amendments to section 421 in section 608(a) of The Family Support Act of 1988 (Pub. L. 100-485 October 13, 1988).

More specifically, under section 421 the employer must (1) provide additional benefits to the employee or retired former employee that are at least equal in actuarial value to the duplicative benefits, (2) refund to the employee or retired former employee an amount of money equal in actuarial value to the duplicative benefits, or (3) provide a combination of additional benefits and refunds that total at least the actuarial value of the duplicative benefits. In computing the actuarial value of the duplicative Part A, benefits (beginning January 1989) and duplicative Part B benefits (beginning January 1990), employers have the option of using national average actuarial values published by the Secretary or calculating the actuarial value based on guidelines published by the Secretary.

[1] Note.—To avoid repetition, the term "employee", when used in this notice, also includes retired former employees.

II. Provisions of This Notice

This notice provides the actuarial values for the benefits added by Pub. L. 100-360; specifies the employers to whom the notice applies; defines "additional benefits;" gives the applicable effective dates; defines duplicative benefits; contains the guidelines for employers to use to compute the actuarial value of duplicative benefits; and lists some of the benefits added by Pub. L. 100-360.

A. National Average Actuarial Value of the Medicare Benefits Added or Increased by Pub. L. 100-360

The national average actuarial value of the Medicare Part A benefits added or increased by Pub. L. 100-360 was $61 as of July 1, 1988. This is the cost of providing the increased Part A benefits for each beneficiary enrolled. Fifty percent of this amount is $30.50 per year. For 1989, the national average actuarial value is $65. The national average actuarial value of the Part B benefits added or increased by Pub. L. 100-360 will be published prior to January 1, 1990.

B. Responsibility of Employers

Employers are responsible for determining if, as of July 1, 1988, they offered to their employees or retired former employees who are covered by Medicare any duplicative Part A benefits (as defined in D. below) and, if so, the actuarial value of any such benefits on July 1, 1988. If the actuarial value of their duplicative Part A benefits was, as of July 1, 1988, 50 percent of the 1989 national average actuarial value of the Medicare benefits added or increased under Pub. L. 100-360 (discounted to the value as of July 1, 1988), the employer is required to offer additional benefits or refunds, or a combination of additional benefits and refunds, equal in actuarial value to the value of the duplicative benefits determined as if they were provided in 1989.

If an employer provides only additional benefits, the benefits must be equal in value at least to the 1989 national average actuarial value of the duplicative Part A benefits that were provided by the employer to employees as of July 1, 1988. Employers may provide a wide range of additional benefits as long as they are equal in value to at least the actuarial value of the duplicative benefits. The additional benefits may consist of health care benefits that do not duplicate the new Medicare benefits and may include payment of the Part B premium, provided the employer was not already

APPENDIX 10:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 444

[Docket No. 79N-0155]

Oligosaccharide Antibiotic Drugs; Neomycin Sulfate for Compounding Oral Products

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the antibiotic drug regulations which describe standards for nonsterile neomycin sulfate for prescription compounding. The amendments change the product name from "neomycin sulfate for prescription compounding" to "neomycin sulfate for compounding oral products" and require labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use. The labeling will state that the product is recommended for oral use only. Elsewhere in this issue of the **Federal Register** is a notice announcing the availability of guideline labeling for neomycin sulfate for compounding oral products and offering an opportunity for a hearing on the proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for nonsterile neomycin sulfate products that are labeled in accordance with the antibiotic regulations. These actions are being taken because nonsterile neomycin sulfate, a prescription drug with a recognized potential for producing toxicity, is now supplied for prescription compounding without adequate labeling. The drug is being used for indications for which it lacks evidence of effectiveness and for which there is clinical evidence of significant risk to the patient. FDA is offering an opportunity for a hearing, under the formal rulemaking provisions in section 507(f) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 357(f)) and the Administrative Procedure Act (5 U.S.C. 556 and 557), on objections to the final rule.

DATES: Effective June 14, 1988; notice of participation and request for hearing by May 16, 1988; data and information to justify a hearing by June 14, 1988.

ADDRESSES: Written comments concerning guideline labeling, requests for copies of the guideline, requests for hearing, and supporting data and information to Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. (Send two self-addressed adhesive labels to assist the Branch in processing your request.)

Requests for opinion of the applicability of this final rule to a specific product to Division of Drug Labeling Compliance (HFN-310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judy O'Neal, Center for Drug Evaluation and Research (HFN-366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8041.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 27, 1979 (44 FR 44178), FDA proposed to revoke the provisions in the antibiotic drug regulations (specifically, § 444.942a) that provide for the certification of nonsterile neomycin sulfate for prescription compounding. This action was proposed primarily because FDA believed that the risks of the drug outweighed its benefits. The nonsterile drug was permitted to be shipped without a package insert identifying approved indications for use and describing adverse reactions and warnings. It was being used for indications for which FDA concluded, in the Drug Efficacy Study Implementation (DESI) project, sterile neomycin sulfate lacked evidence of effectiveness (37 FR 4224; February 29, 1972) and for which there is clinical evidence of significant risk to the patient. These indications include: (1) Intraperitoneal instillations; (2) use in wet dressings, packs, and irrigations to treat secondarily infected wounds and ulcers; and (3) use for intestinal instillation in emergency abdominal surgery. FDA believed that the nonsterile drug was no longer needed for the use for which it was initially made available—for extemporaneous compounding of individual prescriptions by pharmacists—because of the availability of neomycin sulfate in commercially prepared forms.

The agency received 55 written comments on the proposal from physicians, pharmacists, and pharmaceutical manufacturers. All but two of the comments were opposed to some aspect of the proposal. In addition, the agency received three requests for an informal conference. A notice of opportunity for an informal conference was published in the **Federal Register** of October 19, 1979 (44 FR 60331), and an informal conference was held on November 20, 1979. The comment period also was extended for 30 days after the date of the informal conference. The substantive comments and the agency's responses are discussed later in this document.

Based on its evaluation of these written and oral comments and on other information (discussed below), FDA concludes that nonsterile neomycin sulfate should be available for use in compounding oral prescription products. This final rule amends the regulations to change the product name and to require package insert labeling to inform users of the product about the risks associated with neomycin sulfate.

In a notice published elsewhere in this issue of the **Federal Register**, FDA is proposing to withdraw approval, under section 505(e) of the act (21 U.S.C. 355(e)), of the antibiotic applications and abbreviated antibiotic applications that are not supplemented, by the effective date of this final rule, to provide for the new product name and package insert labeling. The agency has prepared guideline labeling that manufacturers and suppliers may adopt to ensure that their labeling complies with the requirements of the revised regulations.

Only neomycin sulfate for prescription compounding is affected by this action. Other preparations containing neomycin, including otic, ophthalmic, oral, and dermatologic dosage forms may continue to be marketed. Elsewhere in this issue of the **Federal Register**, FDA is issuing a final rule based upon its proposal to revoke provisions for certifying sterile neomycin sulfate in vials for parenteral use and is proposing to withdraw approval of applications for those products.

II. Discussion

A. General Observations

Neomycin sulfate has the most potent ototoxic, nephrotoxic, and neuromuscular blocking potentials of the commercially available aminoglycoside antibiotics (Refs. 1 through 11). It also is the most strongly tissue bound. Ototoxicity, nephrotoxicity, neurotoxicity, or a combination of these toxic reactions has occurred following the irrigation of wounds (Refs. 12 and 13), decubitus ulcers (Refs. 4 and 14), joints (Refs. 15, 16, and 17), and fractures (Ref. 13); following intraperitoneal (Refs. 18 and 19), intrapleural (Refs. 20 through 23), mediastinal (Ref. 24), and rectal and colonic lavage (Ref. 25); following infusion into an empyema cavity (Ref. 26); following the use in sinuses (Ref. 27), and in dialysis fluid (Ref. 13); following local applications to prevent burn wound sepsis (Refs. 28 through 31);

following cutaneous applications of impregnated skin grafts (Ref. 32); and following an oral administration (Refs. 19 and 33 through 37). Moreover, substantial systemic absorption following topical administration of neomycin sulfate has been demonstrated (Ref. 38), in many cases by the presence of substantial serum concentrations (Refs. 16, 39, and 40), and at times with fatal outcome (Refs. 17, 18, 24, and 41). Toxicity associated with parenteral use is so great that this route has been essentially abandoned (Refs. 1, 4, 19, 42, and 43).

Indications for the use of neomycin sulfate have changed since it was first approved on March 7, 1951. Because of information about neomycin's toxicity and because less potentially toxic aminoglycosides such as gentamicin, tobramycin, netilmicin and amikacin sulfates now are available for systemic use, neomycin sulfate can no longer be recommended where significant systemic absorption may occur. The monograph for the one remaining indication for systemic use of sterile neomycin sulfate is being revoked elsewhere in this issue of the **Federal Register**. Orally administered neomycin sulfate is indicated only as adjunctive therapy in preoperative preparation of the bowel and in treatment of hepatic coma.

B. Ototoxicity

Deafness due to the parenteral administration of neomycin was first reported in 1950, just a little more than a year after the antibiotic was discovered, in four of six tuberculosis patients (Ref. 44). Shortly thereafter, five more cases were reported (Ref. 37). In each of these five cases, the adverse reaction was not noticed until some time after the treatment was discontinued. As early as 1959, a summary of 20 such cases shows that hearing loss occurred with treatment periods ranging between 3 and 58 days (Ref. 45). Within the next decade, neomycin ototoxicity was found to occur after use of the drug by all routes of administration that were common at the time: parenteral, aerosol, oral, wound and bowel irrigation, and cutaneous application (Ref. 46).

Safe and effective use of neomycin sulfate requires an understanding of its absorption, excretion, and toxicity in the inner ear. The characteristic pattern of neomycin-induced ototoxicity is the loss, which may be massive, of sensory hair cells, both inner and outer hair cells, supporting cells, and neurons (Refs. 19 and 47 through 49). Postmortem examinations of human temporal bones from patients who had received neomycin during peritoneal irrigation, including the temporal bone of a 10-year-old boy who had received only one peritoneal irrigation, showed complete disappearance of the organ of Corti in the basal turn of the cochlea and incipient degeneration of the distal ends of the cochlear nerve fibers in adjacent portions of the osseous spiral lamina (Ref. 19). Otopathologists have reported varying degrees of inner and outer hair cell degeneration and cochlear neuron degeneration in specimens from other patients with neomycin-induced sensorineural deafness (Refs. 47 through 49). The drug's ototoxic effect is not always the same in each patient, presumably because of wide individual variations in systemic absorption from the various routes of administration and because of patient-to-patient variations in the susceptibility of cochlear tissues (Ref. 50).

Polyphosphoinositides, lipids in inner ear tissues that are essential for the regulation of membrane structure and permeability, may be involved in neomycin ototoxicity. It has been suggested that the biochemical basis for neomycin's ototoxicity is the drug's inhibition of the metabolism of polyphosphoinositides (Refs. 47 and 51).

Neomycin, like other aminoglycosides, accumulates and is retained in the inner ear fluid or perilymph. Neomycin's rate of elimination from the inner ear is slower than the other aminoglycosides (Ref. 9) and far slower than its rate of elimination from the serum (Refs. 5, 8, 9, and 47). Significant accumulation of neomycin in the perilymph has been observed in guinea pigs. In one study, a single intramuscular injection of neomycin base, 150 milligrams per kilogram (mg/kg), resulted in a peak drug concentration in the perilymph of 7 to 8 micrograms per milliliter (micrograms/mL) after 3 to 6 hours (Ref. 9). The amount of neomycin decreased so slowly that only one-third had been eliminated after approximately 24 hours, when serum levels were undetectable. Traces of neomycin were detectable in the perilymph for up to 55 hours. When 150 mg/kg doses were repeated daily for 4 days, the concentration of neomycin in the perilymph increased significantly in a stepwise manner to a maximum of 20 micrograms/mL (Ref. 9). The concentration of neomycin in the perilymph did not fall below 1 microgram/mL until 72 hours after the last dose.

In a second guinea pig study, after a single subcutaneous injection of neomycin sulfate, 25 mg/kg, the concentration of neomycin in the perilymph rose to 111 micrograms/mL in 1 hour and was still 10.6 micrograms/mL 25 hours after the injection (Ref. 8). The half-life of the antibiotic in the perilymph was 15 hours, 10 times longer than its half-life in the blood (Ref. 8). Thus, ototoxicity may, to some extent, be explained by neomycin's high concentration in, and slow elimination from, the inner ear fluid. Less toxic aminoglycosides, show substantially lower levels in perilymph and faster elimination (Refs. 8 through 10 and 47). In the guinea pig, as in other species, neomycin also has a special affinity for sensory hair cells in the organ of Corti (Refs. 7 and 52 through 54).

Neomycin-induced ototoxicity was reported by Stebbins and coworkers in two monkeys that received the drug daily by the intramuscular route (Ref. 55). In one animal treated at a dosage of 100 mg/kg/day, neomycin was discontinued after 5 days because of nephrotoxic effects. A moderate hearing loss had developed at high frequencies (20 to 40 kilohertz (kHz)). In the other animal treated with 50 mg/kg/day, the drug was stopped after 15 days when signs of nephrotoxicity developed. Over the following 6 weeks, hearing loss progressed from a moderate loss at high frequencies to total deafness in both ears. The phenomenon of delayed damage to the organ of Corti occurs in other species as well.

Under the stereomicroscope, cochlear lesions in these monkeys showed all gradations of destruction. The organ of Corti in the lower basal turn had completely disappeared. In the upper basal turn, supporting structures were present but both inner and outer hair cells were absent. An abrupt transition to a normal hair cell pattern occurred at the beginning of the middle turn of the cochlea. Radial nerve fibers in the basal turn were missing. Cochlear locations for threshold response were sharply defined and correlated with the extent of hair cell damage and nerve degeneration, the basal turn being the location for the response to high frequencies. Histopathology similar to that found in monkeys has been reported for humans who received therapeutic doses (Refs. 19 and 47 through 49).

In humans, destruction by neomycin of practically all sensory hair cells and some neural tissue, first at the basal turn of the cochlea (the area for hearing high frequency tones), is common (Ref. 19). Low frequency deafness (apical turn of the cochlea) appears last and vestibular involvement is rare (Ref. 50). Unlike renal tubular cells, damaged cochlear hair cells cannot be regenerated. Once hair cell destruction begins, damage

progresses even after dosing has been discontinued (Refs. 4, 5, 19, 47, and 50).

Deafness is usually a delayed-onset adverse reaction but may appear suddenly (Refs. 24 and 49). Neomycin-induced hearing loss may not be apparent until well after the patient has completed the course of treatment (Refs. 35, 39, 40, and 43). Latency periods are usually 2 to 6 weeks after the initiation of treatment and deafness may progress for 6 to 10 months (Refs. 5, 56, and 57). The absence of symptoms and the absence of an abnormal audiogram at the end of therapy do not mean that neomycin-induced hearing loss will not develop later or that it has not already developed at frequencies above 8,000 kHz, higher than conventional audiometer is capable of detecting. Lethargy, headaches, confusion, or tinnitus may occur just before a hearing loss is recognized (Ref. 4). Once symptoms develop, the deterioration of hearing cannot be averted. Serial audiography over a period of 6 to 10 months reveals a gradually progressive, sometimes partial but usually profound, bilateral sensorineural hearing defect (Refs. 5, 20, 22, 28, 33 through 35, 40, 44, 45, 47, 56, and 57). Ototoxicity occurs regardless of age, with or without concomitant nephrotoxicity (Ref. 16), and there is no threshold or dose level below which toxicity cannot be expected to occur (Ref. 22). The ototoxicity of neomycin is additive to the ototoxicity of certain other ototoxic drugs, i.e., other aminoglycosides, vancomycin, polymyxin B, and furosemide (Ref. 57).

C. Nephrotoxicity

The nephrotoxicity of neomycin sulfate is well established (Refs. 1, 4, 10, 15 through 17, 23, 24, 32, 35, 39, 40 through 43 and 58 through 60). Patients with neomycin-induced nephrotoxicity develop sloughing of renal tubular epithelial cells, cylindruria, hematuria, and increased blood urea nitrogen. The renal damage is primarily in the tubules and is manifested as dose-related tubular cell necrosis. Vacuolization of the proximal renal tubular epithelium has also been reported (Refs. 58 and 61).

D. Neuromuscular Blockade

Neuromuscular blockade induced by neomycin sulfate may be manifested in different ways. Coleman and co-workers summarized published reports of respiratory arrest in 12 anesthetized pediatric patients (4 were fatal) that occurred between 10 and 30 minutes after intraperitoneal absorption of neomycin (Ref. 18). Craig and co-workers summarized published reports of severe respiratory depression in 25 patients (8 were fatal) (Ref. 62). Neomycin-induced neuromuscular blockade has been reported as cessation of respiration and coma (Ref. 17); lethargy with progressive flaccidity and coma with dilated pupils after anesthesia (Ref. 18); apnea and unconsciousness 6 hours after irrigation of a septic gunshot wound (Ref. 39); and flaccid extremities, dilated pupils, and intermittent unconsciousness beginning 3 hours after intraperitoneal instillation of neomycin (Ref. 63). In most cases intraperitoneal lavage had been given. Neomycin sulfate is thought to decrease the influx of the calcium ion into the motor nerve terminal, which in turn decreases the output of acetylcholine at the myoneural junction (Refs. 18, 64, and 65). Transmission at this site normally depends on the release of acetylcholine into the synaptic space. This curariform toxicity is similar to that caused by the other aminoglycosides.

E. Adverse Events Reported

Since 1969 FDA's Drug Experience Surveillance Program has maintained a computerized file of spontaneous reports of adverse events associated with the use of neomycin sulfate (Ref. 41). Because these reports come from a variety of sources, the quality of information in the system varies from excellent, e.g., a detailed case summary attached to pages reproduced from a hospital record, to very poor, e.g., a physician's report giving the word "deafness" with no other information. Thus, a causal relationship between neomycin sulfate and the reported adverse event cannot be established with certainty in all cases. However, many of these reports do specify the dosage, the period for which the drug was used, and the route of administration. The following table lists the adverse events reported to FDA that were associated with the use of neomycin sulfate in 194 patients; 17 of these were fatal. It covers the reporting period from 1969, when computerization began, to March 6, 1984.

DRUG EXPERIENCE REPORTS ASSOCIATED WITH USE OF NEOMYCIN, 1969 THROUGH MAR. 6, 1984, ROUTES OF ADMINISTRATION

Adverse reaction	Irrigations	Intramuscular	Intravenous	Intravenous, oral, and rectal	Rectal	Rectal and oral	Unknown	Oral	Ointment	Cream	Ophthalmic	Otic	Total
Ototoxicity alone	31	3				1	11	7					53
Ototoxicity and nephrotoxicity	8	1				1	2	1					13
Ototoxicity and neurotoxicity			2										2
Ototoxicity and nephro- and neurotoxicity	2			1(1)							1		4(1)
Ototoxicity and hypersensitivity or miscellaneous	1	1							1				3
Total ototoxicity													75
Nephrotoxicity alone	3	2(1)	1				1(1)	10(3)					17(5)
Nephrotoxicity and exfoliate dermatitis							1						1
Neurotoxicity alone or with other	6(6)							5(1)					11(7)
Neurotoxicity and nephrotoxicity	1(1)												1(1)
Hypersensitivity alone or with other	7				1		1	13	9	11	1	2	45
Hypersensitivity and GI disorder							2						2
Gastrointestinal	2(1)					1	3	10(1)					16(2)
Other	2		4				4(1)	10	2	1	3	1	26(1)
Total	63(8)	9(1)	5	1(1)	1	3	25(2)	57(5)	11	12	5	3	194(17)

Numbers in parentheses are fatalities.
Three of 4 intravenous cases were inadvertent intravenous administrations of a product compounded for irrigation.

There were 75 reports of ototoxicity. Ototoxicity alone occurred in 53 cases and was accompanied by nephrotoxicity and neurotoxicity in 19 cases. Nephrotoxicity or renal failure was reported 35 times. There were 17 reports of neuromuscular blockade and/or other neurotoxicity. Some of the toxicity experiences may have been due to the additive toxicities of other aminoglycosides, because parenteral kanamycin, gentamicin, streptomycin, or tobramycin sulfates were given concomitantly or sequentially in approximately 13 cases. Twenty-one patients were at risk for additive toxicity due to concomitant irrigation with a fixed or nonfixed combination of neomycin plus polymyxin B (a nephrotoxic and neurotoxic antibiotic) and bacitracin (another nephrotoxic antibiotic). Ototoxicity and nephrotoxicity may have been enhanced in some patients because of the concomitant administration of furosemide and/or ethacrynic acid, both potent, high-ceiling diuretics which are themselves ototoxins.

Of the 17 fatalities, 8 were associated with topical irrigations with neomycin and 5 were associated with prolonged oral use. One such case involved an 11-year-old male who received daily irrigations with 3,000 mL of a 1-percent neomycin sulfate solution to the left hip joint over a period of 8 days for septic arthritis. The boy developed lethargy and cardiac arrest when the hip irrigation system did not drain well. His post-mortem neomycin sulfate blood level was 21.2 micrograms/mL. At autospy his kidney tissue revealed proximal tubular necrosis and his lung tissue showed pulmonary edema.

F. Conclusions: Risk Verus Benefit

The value of using antibiotics in solutions for orthopedic, intraperitoneal, intrapleural, and other surgical wound irrigations to prevent infections remains controversial (Ref. 66). At least one publication states that neomycin should never be used for peritoneal irrigation (Ref. 67). Evidence from the published literature and from FDA's Drug Experience Surveillance Program demonstrates that the use of neomycin sulfate, particularly when appreciable amounts can be absorbed systemically, is associated with significant risk of serious adverse reactions: ototoxicity, nephrotoxicity, and neurotoxicity. These toxic reactions involved prophylactic uses of the drug as well as therapeutic uses. The acceptability of the associated risks with these two types of uses differs slightly: ideally, a prophylactic regimen should be freer from unacceptable and harmful side effects than a therapeutic regimen. An adverse reaction to a prophylactic antibiotic becomes unacceptable when that adverse reaction approaches the seriousness of, or is more serious than, the infection it is intended to prevent or the consequences of that infection.

The benefit of using neomycin sulfate solutions to irrigate surgical wounds has not been demonstrated. In the DESI project, FDA concluded that evidence was lacking to support the effectiveness of sterile neomycin sulfate for such uses. Although some published reports suggest that the local instillation of neomycin during surgical procedures is effective, other publications report that efficacy has not been established. To FDA's knowledge, none of the published reports that recommend the local instillation of neomycin sulfate include followup evaluations long enough after treatment was discontinued to measure the degree of systemic absorption and to determine if delayed-onset, neomycin-induced adverse reactions occurred. Without such long-term followup assessments, clinical reports of the benefits of using neomycin sulfate for wound irrigation must be considered to be incomplete.

Moreover, local antibiotic irrigation at the operative site has disadvantages: (1) Dosage cannot be easily individualized; (2) the antibiotic does not reach the wound until after contamination has begun; (3) distribution is uneven in that the antibiotic does not reach all remote areas in the wound; and (4) systemic absorption cannot be controlled. Generally, delivery of an antibiotic to the tissues at the site of an infection is more efficient by the vascular route following systemic administration.

FDA concludes that the risks of adverse reactions from the use of neomycin sulfate irrigations are significantly greater than any demonstrated benefits.

Safety and efficacy have been demonstrated for a number of less toxic alternatives to the local instillation of neomycin sulfate in surgical procedures. The following antimicrobial agents for injection have approved indications for use during the perioperative period for the prevention of infections: cephalothin, cephradine, cephapirin, cefazolin, cefamandole, cefoxitin, cefuroxime, cefonicid, ceforanide, cefotaxime, ceftriaxone, cefotetan, and piperacillin.

When injected before the operative procedure begins, these beta-lactam antibiotics rapidly diffuse into tissues at the operative site. Bactericidal concentrations are maintained in these tissues and in tissue fluids for the full length of many operations; booster injections based upon the drug's elimination half-life may be given when surgery is prolonged. Aside from reduced toxicity, the advantages of parenteral administration of these beta-lactam antibiotics are: (1) Bactericidal concentrations of the antibiotic are present in the tissues before and throughout the period of greatest contamination; (2) dosage may be individualized based upon the patient's weight, age, and state of renal function; and (3) tissue diffusion is more likely to be complete so that there is uniform distribution of the drug to all areas.

The risk versus benefit considerations are different for orally administered neomycin sulfate. Because systemic absorption is low with oral administration, the risk of toxicity is reduced. Adequate evidence supports the effectiveness of neomycin sulfate oral tablet and oral solution preparations as adjunctive therapy for preoperative suppression of intestinal bacteria and for treatment of hepatic coma. For these two indications only, FDA has concluded the benefits outweigh the risks.

If nonsterile neomycin sulfate is to be available for use in compounding oral products for these two approved indications, the agency has concluded it must be labeled to include warnings about the risks of serious toxicity associated with systemic absorption.

III. Response to Comments

A summary of the substantive comments to the 1979 proposal and the agency's responses follows.

A. General Comments

1. Several comments contended that the proposed revocation of the provisions for certification of neomycin sulfate is not based on sound medical reasoning. The comments claimed that neomycin sulfate is being used safely and effectively, that there is no satisfactory substitute available, and that many lives will be endangered if the drug is removed from the market.

The agency believes that sound scientific data support its conclusion that neomycin sulfate for prescription compounding is being used for indications for which it lacks evidence of effectiveness and for which there is clincial evidence of significant risk to the patient. In addition, the agency does not believe that the comments have offered sufficient data from controlled studies to refute this evidence. FDA provided documented evidence supporting its conclusions in the July 27,

1979, proposal and cites additional evidence in this document.

No situations have been identified in which human lives might be endangered either by the action proposed in 1979 or by the actions in this document. The management of hepatic coma is the only life-threatening condition for which neomycin is indicated. Neomycin sulfate oral products, not affected by the actions in this document, are approved for this condition. Hepatic coma also may be treated with oral preparations of kanamycin or lactulose.

2. Several comments asserted that the proposed removal of nonsterile neomycin sulfate powder is an unauthorized infringement on the professional rights of physicians and pharmacists. The comments stated that not all medications can be administered in dosage or prepackaged forms, not all patients can be treated with manufactured products, and certain emergencies can require extemporaneous compounding. The comments said that physicians today must take advantage of all available scientific information to treat specific medical conditions before them. According to the comments, FDA must permit practitioners to use their best judgment in selecting either a dosage form medication, an oral administration, an extemporaneously prepared compound, or any other medication that may be necessary for the patient's welfare. One comment stated that FDA is, in effect, attempting to regulate surgical procedures.

FDA disagrees that this action is an infringement on the professional rights of physicians and pharmacists, and it is not an attempt to regulate surgical procedures. FDA is requiring labeling for neomycin sulfate for prescription compounding to provide information about its use for conditions for which it has been clinically shown to present significant risk to the patient.

FDA does not regulate the practice of medicine. However, it is FDA's statutory responsibility to determine which drug products are safe and effective and, thus, suitable for prescribing, and to determine what information about the drugs is necessary to permit safe and effective prescribing by the physician. The physician may, as part of the practice of medicine, prescribe an approved drug for an unapproved use and otherwise vary the conditions of use from those approved in the labeling. The physician, therefore, is responsible for making the final judgment about treatment in light of the information in drug labeling and other medical information available to him. FDA believes that good medical practice and patient welfare require that physicians remain free to use approved drugs according to their best knowledge and judgment.

3. One comment contended that there is no proof that neomycin sulfate for prescription compounding is being used for indications other than those approved. Another comment stated that an article cited in the proposal from *Hospital Pharmacy* (Ref. 68) does not say that neomycin sulfate is misused, but praises the effective use of neomycin sulfate for prescription compounding and explains how to prepare it.

FDA advises that reports of inappropriate prescribing of neomycin sulfate, especially those reporting serious adverse reactions, can be found in many medical publications such as those referenced in this document and in the proposal. Such reports also can be found in FDA's drug experience files, in the public comments summarized in this document, and in other communications with FDA. These reports demonstrate that the drug is being used for purposes for which it is neither labeled nor intended. Indeed, the article from *Hospital Pharmacy* cited by the comment had also been cited in the proposal as an example of the kind of information appearing in the scientific literature promoting the inappropriate uses of neomycin sulfate.

4. A comment stated that removal of neomycin sulfate for prescription compounding contradicts FDA's initial reason for approving the drug—to provide pharmacists with pure bulk powder instead of tablets in order to extemporaneously compound prescriptions. Another comment maintained the proposal is contradictory because FDA is proposing to revoke certification of neomycin sulfate for prescription compounding but continues to certify the use of neomycin sulfate when mixed with other ingredients such as polymyxin B sulfate.

FDA is not removing neomycin sulfate for prescription compounding from the market as originally proposed. However, new clinical evidence demonstrating unreasonable risk associated with most uses of neomycin sulfate has become available since neomycin sulfate products were originally approved. Based on its review of the comments received and other information cited herein, the agency now has concluded that (1) neomycin sulfate for prescription compounding can be recommended for compounding preparations for oral use only, and (2) labeling is needed to warn users of the product about the risk of administering the drug under conditions where it may be systematically absorbed in significant quantities.

The agency disagrees that this action regarding the nonsterile neomycin sulfate product is inconsistent with the treatment of approved prepared dosage forms. Each finished dosage form product has its own specific strength, identity, and labeling. The safety and effectiveness of each such formulation are supported by clinical data. Because their dosage regimens have been carefully studied, are very specific, and have been found by qualified investigators to be both safe and effective as recommended, such commercially prepared neomycin sulfate products are preferred. An unlimited variety of preparations could be compounded from nonsterile neomycin sulfate; most such preparations, however, have not been clinically tested for safety and effectiveness. As a result of this action, specific dosage and administration information will be provided for oral neomycin sulfate preparations compounded for the approved indications, suppression of intestinal bacteria and treatment of hepatic coma, for which FDA believes there is adequate evidence of safety and effectiveness.

B. Comments About Medical Uses for Neomycin Sulfate

5. Several comments argued that neomycin sulfate for prescription compounding should not be removed from the market because it is needed as a terminal irrigant before wound closure in patients undergoing major orthopedic surgery, particularly total hip replacement, and in irrigating wounds during other surgical procedures. The comments said that this solution has been in use for some time and no adverse effects, including ototoxicity and nephrotoxicity, have been reported by practitioners who follow their patients for an extended period of time.

The agency disagrees. Use of neomycin sulfate for prescription compounding to prepare irrigation solutions lacks evidence of effectiveness and presents significant risk to the patient. The National Research Council of the National Academy of Sciences reviewed the efficacy of neomycin sulfate sterile powder for its labeled indications, including irrigation, as part of the DESI project. After extensive scientific review, the agency published its conclusions about that product's effectiveness on May 13, 1970, and February 29, 1972 (DESI 7837). Neomycin sulfate sterile powder was found effective only for treatment of certain urinary tract infections when

administered by intramuscular injection. Evidence of effectiveness was found lacking for all other claims, including intraperitoneal instillation, use as wet dressings, packs, or irrigations, treatment of varicose ulcers and eye infections, and intestinal instillation in emergency abdominal surgery. The agency considers these conclusions to be equally applicable to the use of the nonsterile powder for compounding formulations intended for the same indications.

FDA believes that there also is a lack of substantial evidence of safety for use of the drug in irrigations during orthopedic surgery (Refs. 12, 13, 15, 16, 27, 38, 41, and 59). Irrigation results in systemic absorption leading to substantial serum and tissue levels. Also, the drug is unevenly distributed at the operative site. Davia reported neuromuscular blockade, renal failure, and a permanent 90 to 95 decibel bilateral hearing loss following one single irrigation of a complicated fracture site in an 18-year-old male (Ref. 39).

6. Several comments argued that neomycin sulfate for prescription compounding should be available for use in augmentation mammaplasty and in the use of other silicon-rubber implants or other prosthetic devices, and as a solution to soak bone grafts prior to implementation. One comment said that neomycin sulfate is used to prevent wound infection in patients undergoing renal transplantation. Another comment noted that "Wynn's solution" containing neomycin, chloramphenicol and polymyxin B has been dispensed for irrigation. According to another comment, neomycin sulfate is used as a prophylactic topical application for foreign prosthetic devices.

The agency concludes that soaking a device or an organ such as above graft in a neomycin sulfate solution may suppress the growth of some microorganisms but will not sterilize the device or organ as contended by the comment. Devices for implantation, such as heart valves, artificial joints, other prostheses, and miscellaneous implants, are usually supplied by the manufacturer in a sterile state or are maintained in a sterile environment. When devices and organs that are left in place after an operation continue to provide open avenues for bacterial colonization or entry, parenteral antimicrobial agents should be considered for prophylaxis.

The agency considers the use of neomycin sulfate solution to soak bone grafts and silicone-rubber implants prior to surgical implantation, and the use of neomycin in an antibiotic solution for the prophylactic topical application to prosthetic devices, to be investigational. In these procedures, large quantities of the antibiotic are disseminated systemically after the solution is instilled in the patient's tissues, and there are inadequate data to establish safe dosage under these circumstances.

7. One comment argued that a 1-percent neomycin sulfate irrigant should be available for use in the bladder following routine instrumentation. The comment's author knew of no harmful effects from this procedure and said that, before FDA withdraws the drug, a double-blind clinical trial should be carried out.

The agency agrees that clinical investigation is needed to provide data on the efficacy, as well as safety, of neomycin sulfate as the single active ingredient in a bladder irrigant product but disagrees that such an investigation is needed before issuance of this final rule. Because there apparently is little or no systemic absorption of neomycin when it is used for irrigation of the intact urinary bladder, toxicity from urinary bladder irrigation generally may not be a problem. (Substantial systemic absorption accompanies irrigation of other sites.) The commercially prepared product containing a fixed combination of neomycin and polymyxin B for bladder irrigation, for which adequate evidence of safety and effectiveness exists, is not affected by this action.

8. One comment argued in favor of the use of a 1- or 2-percent neomycin sulfate irrigating solution in the peritoneal cavity and the use of a 5-percent solution in contaminated sinus wounds. The comment maintained that the risks of ototoxicity and nephrotoxicity are dose related, and that if the proper concentration and dosage are used and the solution is adminstered properly, the drug is safe. Another comment stated that a neomycin sulfate solution is used as a quick method to sterilize fecal spillage in the abdominal cavity and to help sterilize a ruptured appendiceal abscess where systemic antibiotics would not. Another comment noted that a neomycin sulfate solution is used to sterilize a staphylococcal infection in a hernia with Marlex mesh and to help heal a total gastrectomy with a thoracoabdominal fistula.

The agency believes that no concentration and dosage of neomycin sulfate for the irrigation purposes described in these comments has been shown to be safe. There is evidence that significant absorption takes place with these irrigations. Neomycin sulfate solutions, when used to irrigate operative sites, can be very toxic and have caused deaths (Refs. 17, 24, and 41). Even after a single irrigation, neomycin sulfate can be absorbed in amounts substantial enough to produce toxicity (Ref. 39). Systemic absorption that follows irrigation of the peritoneum with these concentrations of neomycin sulfate is equivalent to that which follows a parenteral injection. Furthermore, this route of administration lacks the dosage control of an injection. Once neomycin is absorbed, although the greatest fraction of the dose is rapidly excreted by the kidneys, a high level rapidly develops in the inner ear fluids where the drug is eliminated very slowly over a period of weeks. Applying suction after topical instillation cannot be relied upon to remove the aminoglycoside (Ref. 69), because a significant portion of the drug will have already circulated to both the cochlea and the renal cortex by the time suction is applied. There have been reports that, even though the patient experienced early adverse reactions, neomycin irrigations were continued without the prescriber's being aware that adverse reactions were neomycin induced (Refs. 13, 16, and 17).

The thick wall of an empyeme cavity does not prevent absorption following instillation of neomycin sulfate solution. Meakins reported profound respiratory failure and renal failure following instillation of 1,000 mL of a 1-percent solution in the thoracic cavity of a patient with recurrent empyema who was already totally deaf because of aminoglycosides (Ref. 23). Other authors have reported severe ototoxicity from intrapleural use of neomycin sulfate (Refs. 21, 22, and 26). Gruhl reported a case of renal failure, deafness, brain lesions, and death following 11 days of irrigation of the mediastinum with 2.4 liters (L) of 0.3-percent neomycin solution every 24 hours (Ref. 24).

9. One comment argued that neomycin sulfate is needed in neurosurgical procedures, to irrigate closed space infections, such as those that rarely occur following the removal of an intervertebral disc, and for both intracranial and spinal operations, especially if contamination is thought to have occurred. The comment stated that a 1 mg/mL (0.1-percent) concentration of the nonsterile powder is used to prepare a solution that is subjected to microfiltration followed by autoclave sterilization. The comment stated that concentrations less than 10 mg/mL have been found to be safe, and that a 0.1-percent solution is nonepileptogenic and does not produce cortical depression. The comment added that, although there have not been well-controlled efficacy studies, the widespread use of neomycin

sulfate attests to its acceptance by neurosurgeons and that it is questionable whether truly controlled trials could be conducted.

The agency does not have data from studies in humans to support the safety and efficacy of the local use of neomycin sulfate in the irrigation of closed place infections such as those mentioned in this comment. Concentrations of less than 10 percent, which the comment stated had been found to be safe, were nonepileptogenic, and did not produce cortical depression, appear to have been tested in only three cats (Ref. 70). Six concentrations were tested. Because blood-brain barriers for cats differ from those for humans and effects may be different when tissues are inflamed, these results cannot be applied directly to humans. The study fails to consider individual variations in human tolerance. Although no effects were seen with concentrations of 0.01 percent, and minimal changes were seen at 0.1 percent, locally applied neomycin sulfate in higher concentrations depressed electrocortical activity in cats and produces an inflammatory reaction in the brain as demonstrated by histological studies. Also, neomycin sulfate did produce epileptogenic activity at a higher concentration. Finally, local application of the drug to feline or human neutral tissue has not been evaluated, weeks after treatment ended, for delayed-onset ototoxicity.

FDA agrees that it would not be easy to conduct the usual kind of randomized controlled efficacy trials for these neurosurgical procedures. However, under the law testimonial statements, such as the one in the comment claiming that the widespread use of neomycin attests to its acceptance by neurosurgeons, cannot be substituted for the scientific data required to establish safety and effectiveness. Furthermore, the prophylactic use of antimicrobial agents in neurosurgery is not recommended (Refs. 66 and 67).

10. One comment urged that neomycin sulfate be available for use in staged colonic resections, to prepare the distal defunctionalized portion of the colon by administering a neomycin sulfate irrigant through the distal colostomy and the rectum. The comment cited numerous articles that, according to the comment, substantiate the safe and effective use of neomycin sulfate when proper dosage and administration are followed. The comment stated that in 15 years of using neomycin sulfate, only one patient became deaf, and this was because large doses of neomycin sulfate had been orally administered to a patient with ulcerative colitis. Another comment maintained that neomycin colostomy irrigations are useful for patients with obstructing lesions of the intestinal tract that may prohibit the use of oral antibiotics.

FDA considers the administration of neomycin sulfate through a colostomy site or through the rectum to be investigational. These routes of administration are not included in the labeling for neomycin products because safety and efficacy data are lacking. The agency has reports that total irreversible bilateral deafness has followed neomycin sulfate irrigations of the distal colon and rectum (Ref. 41).

Although the short-term oral administration of neomycin sulfate can be relatively safe, neomycin should not be considered a nonabsorbable antibiotic in the gastrointestinal tract. Approximately 3 percent of an orally administered dose is excreted by the kidney (Refs. 40 and 71). Oral administration has led to significant drug levels in blood and has been associated with ototoxicity (Refs. 19, 33 through 36, 41, and 56). Even the absorption of small amounts of neomycin that result in relatively low serum levels can produce ototoxicity because of drug accumulation and retention in the inner ear if the exposure is prolonged over weeks to months. There may be an increased risk of toxicity if damage to the gastrointestinal tract occurs or if surgical intervention results in increased absorption. In cases of intestinal obstruction or renal impairment, serum levels following oral administration may exceed levels attained after parenteral administration. Ruben and Daly reported profound deafness in a 45-year-old female 1 month after just two oral doses (total 11 grams) given prior to a right colectomy for a partial small bowel obstruction. She became anuric, then noticed a hearing loss 8 days after the first dose (Ref. 35).

11. Several comments contended that irrigation solutions combining neomycin sulfate, bacitracin, and polymyxin B sulfate are both safe and effective, and that these drugs are frequently combined in irrigation solutions for renal transplantation, for orthopedic surgery, for burn therapy, for neurosurgery, and for other surgical specialities.

Orthopedic surgeons, neurosurgeons, and surgeons specializing in the treatment of burns have reported serious toxicities, including bilateral permanent deafness, resulting from the use of this triple combination. Absorption from wounds and granulating surfaces is significant; serum concentrations are comparable to and often higher than those attained with intramuscular therapy. Davia and co-workers reported total permanent bilateral deafness and renal failure following irrigations of orthopedic wounds with these three ingredients in two patients, one having only a single irrigation (Ref. 39). Hemodialysis was required for the other patient who experienced not only permanent deafness but also acute neuromuscular blockage. Bamford and Jones reported deafness in six children ranging in ages from 8 to 16 months following treatment for full-thickness burns with topical sprays containing neomycin, bacitracin, and polymyxin B or E (Ref. 28). Gelman and co-workers reported acute renal failure during the immediate postoperative period on 8 of 41 patients who underwent total hip replacement in which a neomycin-bacitracin-polymyxin B irrigating solution was used twice during the procedure (Ref.15). Little and Lynn reported that a burn covering only 10 percent of the body surface area was treated with an aerosol combination of neomycin, bacitracin, and polymyxin, and the patient became deaf in 17 days (Ref. 30). Graham reported bilateral sensorineural deafness in a 5-year-old girl treated with an aerosol mixture of neomycin, bacitracin, and polymyxin for burns over 80 percent of her body surface (Ref. 31). Rwylin described three cases of extensive necrosis of the epithelium of the proximal convoluted tubules following a single intraperitoneal instillation of 50,000 units of bacitracin and 0.5 g of neomycin. The author suggested that both antibiotics contributed to the tubular damage because both are nephrotoxic and have produced similar lesions individually (Ref. 72).

Labeling for all three of these antibiotics indicates that each one is potentially nephrotoxic. Updated labeling for the aminoglycosides (netilmicin, amikacin, gentamicin, tobramycin, kanamycin, streptomycin, and oral neomycin) even includes box warnings that concurrent and/or sequential systemic or topical use of other potentially neurotoxic and nephrotocix drugs, including bacitracin and polymyxin, should be avoided.

The labeling for polymyxin B sulfate and neomycin sulfate also warns that both products are ototoxic. In addition, neomycin is the most potent neuromuscular blocking aminoglycoside, and polymyxin B sulfate is a potent neuromuscular blocking polypeptide. Their neuromuscular blocking potentials are additive not only in terms of potency and duration but also in terms of the

characteristics of the blocks produced (Ref. 63). The combination product Neosporin® G. U. Irrigant, containing neomycin sulfate and polymyxin B sulfate, is approved for use as an irrigation solution of the intact urinary bladder, where systemic absorption is minimal.

The agency concludes that the concurrent or sequential use of these products should be avoided where systemic absorption may occur.

12. One comment objected to the proposal because neomycin sulfate for prescription compounding is used in the care of severely burned patients. The comment argued that although there is a chance of drug toxicity in these cases, prohibiting the use of the drug would be far worse.

FDA disagrees with this comment because of evidence of toxicity resulting from such use (Refs. 28 through 32) and because of progress in the control of post-burn sepsis without the use of neomycin sulfate. The goal in treating most full-thickness burns of significant size is to reduce the risk of infection. Adequate primary therapy consists of prompt removal of necrotic tissue and immediate closure with biological dressings such as allographs and autographs (Ref. 42). Selection of either the appropriate parenteral antibiotic or the appropriate local therapy for infected burns is based upon the specific contaminating organisms and the safety of the drugs. The antimicrobial agent not only must be effective against the isolated pathogens, but also must be locally and systemically nontoxic if it is absorbed. Two of the topical agents that have approved labeling indications for the management of burn wounds are silver sulfadiazine, and mafenide acetate.

Local instillation of neomycin in open burn wounds results in significant absorption and systemic toxicity. There is no evidence to support the routine prophylactic use of neomycin in major burn injury (Ref. 73). The use of burn dressings impregnated with aminoglycosides has been associated with the development of bacterial resistance and toxicity (Ref. 1). Sugarbaker reported permanent deafness and nephrotoxicity following 29 days of local applications of porcine skin xenographs commercially impregnated with neomycin in the treatment of a partial thickness burn involving 35 percent of the body surface (Ref. 32). As discussed in the preceding paragraph, Bamford and Jones reported severe reactions in six children following the use of topical antibiotic aerosol sprays containing neomycin sulfate, polymyxin B, and bacitracin for the treatment of full-thickness burns covering body surface areas ranging from 10 to 22 percent. All six children developed delayed-onset deafness. Three developed renal failure and three developed tetany associated with a metabolic imbalance (Ref. 28).

13. One comment reported using both nonsterile and sterile neomycin sulfate in the preparation of topical gels, ointments, and sprays as part of the prophylactic regimen for patients undergoing cancer chemotherapy in protected-environment units. The comment stated that neomycin sulfate is compounded with vancomycin, polymyxin B, and nystatin in a topical ointment, and with vancomycin and polymyxin B in a spray.

These uses of these products are outside the scope of this rulemaking and are investigational. Before these uses can be approved and included in the INDICATIONS section of a product's labeling, data on their safety and effectiveness must be submitted for evaluation.

14. Comments from two pediatricians who treat children with chronic lung disease, especially cystic fibrosis, stated that one form of therapy used is an aerosol inhalation, and that neomycin sulfate is used in the aerosol. The comments stated that, theoretically, neomycin sulfate suppresses *Staphylococcus aureus*, a major component of the bacteria in children with this disorder. Another comment noted that there is no conclusive evidence that this form of therapy is particularly effective in suppressing the growth of this organism, but contended that it is accepted therapy and has never been shown to be harmful. The comment said that the drug should remain in use until studies are performed that show it is ineffective.

FDA disagrees with the comment that aerosol inhalation of neomycin has never been shown to be harmful. Neomycin has been reported to be absorbed in toxic amounts by this route. As early as 1960, Fuller reported deafness in two children resulting from the aerosol inhalation of neomycin for the treatment of staphylococcal infections (Ref. 20).

15. Several comments argued that neomycin sulfate for prescription compounding should not be removed from the market because of its use in the preparation of enemas and in compounding oral dosage forms. The comments cited the following as conditions appropriate for treatment with neomycin sulfate enemas: hepatic encephalopathy or coma, cirrhosis, colostomy surgery, biopsy of the prostate, Reye syndrome, and the preoperative preparation of the bowel. In addition, the comments cited the following as conditions appropriate for treatment with oral dosage forms: colon and rectal operations, preoperative bowel preparation, and hepatic coma. One comment asserted that neomycin sulfate in tablet and solution formulations has been used successfully since 1945 to sterilize the colon prior to resection and in other types of intestinal surgery. Another comment stated that neomycin sulfate enemas should be permitted because they are useful for patients who are unable to take medications orally.

The agency does not believe that neomycin sulfate can be recommended for use in the preparation of enemas. Adequate clinical data on the extent of absorption, safe dosage ranges, safe treatment periods, and drug effectiveness after rectal administration are not available. Breen and co-workers studied absorption following oral and enema administration and concluded that "enema-administered neomycin is absorbed to the same extent as that administered orally, and intestinal ulceration does not enhance neomycin absorption" (Ref. 74). However, this one report is not adequate to provide detailed prescribing information for this route of administration. Clinical evidence concerning the safety or effectiveness of neomycin sulfate used as an enema in the treatment of Reye syndrome also is unavailable.

Although there is significant systemic absorption following the local instillation of neomycin sulfate in the peritoneal cavity and other tissues during surgery, the agency believes that the short-term oral administration of the drug can be relatively safe. Neomycin sulfate is poorly absorbed from an intact gastrointestinal tract following oral administration. Currently available oral tablets and oral solutions will not be affected by this action. The current labeling for these oral products recommends their use as adjunctive therapy for the suppression of intestinal bacteria as in the preoperative preparation of the bowel and for the treatment of hepatic coma for periods up to 3 weeks. (Oral tablets should not be instilled into an operative site. FDA has received a report about a patient who lost her hearing following the instillation of two neomycin tablets directly into an infected postoperative cholecystectomy wound twice daily for 8 days.) The agency agrees that neomycin sulfate should be available to compound prescriptions for oral use for the two approved indications. Compounded oral

solutions may be useful for patients who are unable to take solid dosage forms.

16. One comment stated that, although neomycin sulfate is not approved for enema use in the treatment of hepatic encephalopathy, there is no other antibiotic that has been approved for this use that has low toxicity and is economical to the patient. The comment asserted that kanamycin, a possible alternative, is not approved for enema use and is much more toxic, and that the only dosage form available for compounding is the injectable product which is very expensive. Other comments noted that lactulose, another drug which may be used instead of neomycin sulfate as an enema preparation in patients in hepatic coma, may not be effective in some patients and has not been approved by FDA for this indication.

FDA notes that, although kanamycin is not approved for enema use in the treatment of hepatic coma, it is approved for oral administration. Kanamycin sulfate, an aminoglycoside closely related to neomycin with similar ototoxic and nephrotoxic potentials, is slightly less toxic than neomycin sulfate (Refs. 2, 5, 6, 11, 22, 42, 43, 50, 55, 75, and 76). Kanamycin-induced hearing loss also can be rapid in onset, progressive, and severe, can occur after the administration of small quantities, and may continue to develop after cessation of treatment (Ref. 2). Its absorption from the gastrointestinal tract is about 1 percent, however, less than the 3-percent systemic absorption of neomycin (Ref. 43), and its rate of elimination from the inner ear is faster (Ref. 9).

Although slightly less ototoxic, kanamycin, like neomycin, first attacks the outer hair cells of the basal turn of the organ of Corti. Neomycin sulfate, however, destroys both the outer and inner hair cells and distal ends of the fibers of the cochlear nerve, as well as most of the supporting cells, and affects all turns of the cochlea (Ref. 13). With kanamycin there is said to be nearly complete preservation of nerve fibers despite outer hair cell loss, and the progression of kanamycin-induced hearing loss may be arrested, or in a few patients reversed, by terminating therapy after the first signs of ototoxicity appear (Ref. 47). As with all aminoglycosides, impaired renal function potentiates this effect. The labeling for kanamycin sulfate oral capsules states that the capsules are indicated when suppression of the normal bacterial flora of the bowel is desirable for short-term adjunctive therapy, and for treatment of hepatic coma.

Lactulose syrup, contrary to the comment, is approved by FDA for oral and rectal administration for the prevention and treatment of portal-systemic encephalopathy, including hepatic pre-coma and coma states. When compared in a controlled double-blind clinical trial in the treatment of hepatic encephalopathy, both lactulose and neomycin sulfate were equally effective (Ref. 77). The *AMA Drug Evaluations* indicates that lactulose is preferred for long-term therapy because of its lower toxicity (Ref. 1).

17. One comment argued that commercially prepared dermatologic drug products should not completely replace extemporaneously prepared products made with neomycin sulfate for prescription compounding. The comment stated that dermatologists, particularly in high volume clinics, frequently have uniquely formulated products. Another comment stated that the risk of adverse side effects is greatly diminished when neomycin sulfate is topically applied, and that neomycin sulfate for prescription compounding should be permitted to remain on the market with a label restricting its use to dermatological applications only. The comment maintained that approximately 15 percent of the neomycin sulfate powder sold is used for dermatological preparations and that removal would cause an unjustified hardship. The comment added that if FDA would permit the product to be marketed only in 100-g containers with modified and restricted labeling, the agency would have easy access to records of the product being shipped and would be in a better position to monitor unapproved uses.

FDA notes that there are many commercial preparations containing neomycin sulfate that are already available for dermatologic, ophthalmic, or otic use, and also one for urological use. This action will not affect the availability of bulk neomycin sulfate that is supplied to pharmaceutical manufacturers for use in making these specific dosage forms. With the revocation of provisions for certification of (and withdrawal of approval of applications for) neomycin sulfate sterile powder, the only remaining prescription products in which neomycin sulfate is the only active ingredient will be neomycin sulfate oral tablets and solution and, as discussed below, neomycin sulfate for compounding oral products. There is adequate evidence of the safety and effectiveness of these approved products for their labeled indications, suppression of intestinal bacteria and treatment of hepatic coma. Adequate evidence is not available, however, to support the agency's approval of the use of nonsterile neomycin sulfate for extemporaneously compounded preparations other than for oral use.

If nonsterile neomycin sulfate is to remain available it must be labeled to provide full prescribing information for safe use of the product. "Neomycin sulfate for prescription compounding," to be renamed "Neomycin sulfate for compounding oral products," will be required to have package insert labeling, including warnings and the same indications for which the oral tablets and solution are approved. Additional indications may be added to the labeling when a supplement containing adequate evidence of their safety and effectiveness is submitted and approved.

18. Several comments referred to the use of specific concentrations of neomycin sulfate irrigation and enema solutions, contending that the risks of ototoxicity and nephrotoxicity are dose related and that, if the proper concentration and dosage are used and if neomycin is administered properly, the antibiotic is safe. One comment said that tentative guidelines for irrigating solution concentrations and usage should be developed.

The agency has concluded that no specific concentrations of neomycin sulfate irrigation and enema solutions can be recommended as safe and effective without further study. Serious permanent toxic reactions have been reported in the medical literature following the use of concentrations ranging from very dilute to as high as 10 percent (Ref. 27). In published reports of local irrigations, the amount of the drug used has almost always greatly exceeded what appears to be necessary. (See the response to comment 8, above.) A 1-percent concentration is often 1,000 times greater (range = 16 to 2,000 times greater (Ref. 10)) than most mean inhibitory concentrations needed in vitro to eradicate the expected microorganisms (Refs. 10, 42, and 50). Weinstein demonstrated that striking systemic absorption occurred in all 10 patients undergoing hip replacements who received single 5- to 20-minute local irrigations with a 1-percent neomycin solution (Ref. 38). Irrigating volumes were small, varying from 500 to 1,150 mL with a neomycin dose range of 66.7 to 202.7 mg/kg. These doses are 4 to 13 times those previously recommended for parenteral use. Peak serum concentrations (up to 15.5 micrograms/

mL) were attained in 5 of the 10 patients by 15 to 30 minutes and in 4 others by 1 hour. Serum concentrations at 2 hours ranged from approximately 1.2 to 10 micrograms/mL, and at 4 hours all remained higher than 1.2 micrograms/mL. Two patients had concentrations above 9 micrograms/mL at 4 hours. In other reports, these serum levels of neomycin have been associated with nephrotoxicity and ototoxicity (Refs. 16 and 39).

FDA does not agree that guidelines for irrigating solutions should be developed. Because safety and effectiveness have not been established for the use of neomycin sulfate in irrigating solutions, even very dilute solutions, the agency cannot make recommendations about dosage and administration.

C. Comments With Labeling Suggestions

19. Several comments recommended other ways to safeguard against the toxicity problems associated with neomycin sulfate for prescription compounding rather than withdrawal of the drug from the market. Some of the recommendations were to: (a) Provide label and package insert contraindications and warnings; (b) include in the labeling all indications for which similar products are approved, i.e., ophthalmic, otic, oral, and topical, including dermatological, uses and include directions for these uses; (c) continue to certify the product pending final resolution of an appropriate package insert.

FDA agrees with the comments recommending complete labeling for neomycin for prescription compounding and has not withdrawn the product pending resolution of guideline labeling. However, FDA does not believe that it has a basis for including labeling for all the indications for which products containing neomycin sulfate are approved and are readily available. Except for neomycin sulfate oral tablets and solutions, all prescription products containing neomycin sulfate are fixed combinations that also contain one or more other active ingredients. Approval of a fixed combination for a specific indication does not provide the basis for approval of one of the ingredients alone for the same indication. Effectiveness of a fixed combination is based upon the antimicrobial activities of specific quantities of two or more antimicrobial agents added together. The agency is not aware of data that establish the safety and effectiveness of neomycin sulfate alone for any indication in prescription drug labeling except for the indications in the approved labeling for the oral neomycin products.

20. One drug manufacturer commented that the proposal failed to mention that the Anti-Infective Agents Advisory Committee recommended immediate inclusion of a boxed warning on the product's labeling that would emphasize the drug's ototoxicity and nephrotoxicity potentials, and that the proposal also failed to mention the committee's conclusion that pharmaceutical manufacturers should be contacted to add to the boxed warning.

Another comment recommended that a package insert and a boxed statement on the container label be used to provide pharmacists and physicians with adequate information on the risks involved. Because the drug has a fairly large container, the comment added, there is ample room on the existing label to put a boxed warning statement to warn about absorption and to request that the accompanying package insert be read. The comment stated that neomycin sulfate should be permitted for use in irrigating solutions and that the physician should be permitted to make a benefit-risk judgment concerning the use of neomycin sulfate in these and other circumstances where significant systemic absorption may occur.

FDA notes that the proposal did state that a boxed warning was recommended by the Anti-Infective Agents Advisory Committee for neomycin for prescription compounding (44 FR 44178 at 44179; July 27, 1979). However, the proposal also explained that because the product was shipped in bulk for prescription compounding, it was permitted to be shipped without a package insert that would have described approved indications for use, adverse reactions, and warnings. Moreover, pharmaceutical manufacturers were contacted and given an opportunity for input when FDA provided for a comment period on the proposal, when FDA held an informal conference November 20, 1979, and when the comment period was extended at the manufacturer's request.

Because the drug is being used for indications for which it lacks evidence of effectiveness and for which there is clinical evidence of significant risk to the patient, FDA believes that neomycin sulfate can no longer be permitted to be shipped without adequate labeling. FDA agrees that a package insert is needed to provide pharmacists and physicians with the information necessary for the safe and effective use of the drug, including its potential hazards. A boxed warning on the container label, although a step in the right direction, would be too brief to provide essential scientific information that is needed for the safe and effective use of the drug (21 CFR 201.56). The following sections from the specific requirements on the content and format of the labeling (21 CFR 201.57), are applicable to aminoglyoside antibiotics: description, clinical pharmacology including microbiology, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, dosage and administration, how supplied, and if appropriate, animal pharmacology and/or animal toxicology.

FDA's labeling guideline for neomycin sulfate for compounding oral products provides the required information. The guideline states first that the product is not for intra-operative irrigation and other parenteral use. A boxed warning describes the ototoxic and nephrotoxic reactions that have been reported following parenteral, aerosol, and oral administration, topical application to wounds, bowel and surgical irrigation, and other uses. The warning advises that renal impairment is not a prerequisite for ototoxicity and that ototoxicity is not always dose-related. In addition, the WARNING section states that neuromuscular blockade and respiratory paralysis have been reported following the use of neomycin.

The guideline advises that because fatal and irreversible toxic reactions may follow the local instillation of neomycin during surgical procedures and the local application of neomycin to full-thickness burns, these routes of administration should be avoided.

The INDICATIONS section of the labeling guideline states that oral neomycin is indicated as adjunctive therapy (1) as part of a regimen for preoperative suppression of normal bacterial flora of the bowel and (2) in hepatic coma. This section also includes a statement that evidence of safety and effectiveness is lacking for the administration of neomycin through the distal portion of the colon in staged colonic resection and through the rectum as an enema to treat acute hepatic coma.

In requiring labeling to provide information concerning appropriate uses and to warn about the risks of inappropriate use, FDA is not preventing any physician from making his or her own benefit-risk judgments about the use of neomycin. A physician's decision to use an approved drug in a given situation does not depend solely upon whether or not that use is indicated in the labeling.

D. Other Comments

21. One comment, contending that neomycin sulfate is approved by FDA as

an irrigant, referred to an FDA-approved package insert for Neosporin® G. U. Irrigant, an irrigation solution consisting of a combination of neomycin sulfate and polymyxin B sulfate. The comment noted that polymyxin does not reduce any of the alleged toxic effects of neomycin sulfate. The comment also requested copies of scientific studies that prove neomycin is absorbed when used in irrigating solutions.

Neosporin® G. U. Irrigant is a fixed combination approved by FDA for use as an irrigation solution of the intact urinary bladder. One mL (containing neomycin sulfate equivalent to 40 mg neomycin base and 200,000 units of polymyxin B sulfate) is to be diluted in 1,000 mL isotonic saline solution. When the urinary bladder is intact, systemic absorption of the prepared solution is minimal. Approval of this fixed combination product does not provide the basis for approval of neomycin sulfate for prescription compounding for this indication. Efficacy of the fixed combination, based upon the antimicrobial activities of specific concentrations of two antibiotics, is broader than that of each of the two active ingredients alone. The data used by the agency to conclude that Neosporin® G. U. Irrigant is safe because it is not absorbed from the intact urinary bladder, and that it is effective as an irrigation solution, are different from the data that would be required to demonstrate the safety and effectiveness of a given concentration of neomycin sulfate as a single-ingredient irrigation preparation.

Regarding the request for copies of studies, there are many published reports of absorption following neomycin sulfate irrigation, some of which are included in the reference list in this document.

22. One comment stated that FDA has asked companies that manufacture or sell neomycin sulfate for prescription compounding to produce scientific studies to show its safety. The comment said that of all the aminoglycosides on the market today, only neomycin sulfate is no longer patented. Therefore, the comment claimed, no company will expend large amounts of money to prove the safety of the drug because that company would have no exclusive rights to its product. The comment argued that it is inconsistent for FDA to request such studies because the agency must already have such data in support of the approved package insert for Neosporin® G. U. Irrigant, which contains neomycin sulfate as a component. The comment stated that the same data used by FDA in approving a product that contains neomycin sulfate as a component should apply to neomycin sulfate for prescription compounding. The comment also noted that the package insert for Neosporin® G. U. Irrigant includes the following contraindication: "This product is contraindicated in those individuals who have shown hypersensitivity to any of its components." The fact that Neosporin® G. U. Irrigant has such a contraindication, the comment argued, should require that neomycin sulfate for prescription compounding remain on the market, because a solution of neomycin sulfate in its pure form would still be available for a patient who shows hypersensitivity to polymyxin B sulfate.

FDA believes that if there is actually a need for neomycin sulfate as a component in an enema or irrigation solution, manufacturers will be economically motivated to conduct the scientific studies or submit the published reports that are necessary to demonstrate its safety and effectiveness in these products. Concerning the comment's statement that FDA already has safety and effectiveness data for Neosporin® G. U. Irrigant, the agency advises, as stated in the response to comment 21 above, that these data are different from the data that would be required to establish the safety and effectiveness of neomycin sulfate alone. The data supporting Neosporin® G. U. Irrigant are from studies on a finished, fixed-combination dosage form containing both neomycin sulfate and polymixin B sulfate. These data are not applicable to nonsterile neomycin sulfate for prescription compounding because the effectiveness of the combination product results from the antimicrobial activities of specific quantities of the two antibiotics together. In addition, the required prescribing information regarding appropriate dosing and administration is lacking for the use of neomycin sulfate as a single ingredient product for irrigation of the bladder for polymyxin B sulfate-hypersensitive patients. Information regarding dosage and administration is particularly important for neomycin because of its known toxicity.

23. Noting that the proposal stated that neomycin sulfate was approved in 1964 as a dermatological preparation, one comment disagreed that neomycin sulfate for prescription compounding was ever used as a dermatologic preparation. The comment stated that FDA provided for batch certification of neomycin sulfate in response to a petition filed by the American Society of Hospital Pharmacists (ASHP). The comment enclosed a copy of the ASHP petition requesting the approval of neomycin sulfate as (1) a solution for wet dressings, (2) a solution for irrigation, (3) an ophthalmic medication of various strengths, (4) an ophthalmic medication using different ointment bases, and (5) a medication prescribed for individual patient needs. The comment concluded that, originally, dermatologic uses were not even discussed.

FDA disagrees with this comment. The original applications for neomycin sulfate sterile vial, approved by FDA on March 7, 1951, indicated that one of the uses for the drug was as an ointment for the topical treatment of skin infections in both humans and animals. In addition, the September 19, 1963, petition from ASHP also stated that a need existed for several compounded medications including "neomycin sulfate ointments in special bases professionally preferred by dermatologists."

24. Several comments contended that removing neomycin sulfate for prescription compounding from the market will not stop the uses of neomycin sulfate that the proposal is intended to prevent. One comment noted that the proposal would remove from the market only the bulk and the injectable neomycin sulfate, leaving neomycin sulfate as an oral solution, in tablet form, and in other products which have neomycin sulfate as a component. The comments contended that physicians who prefer to continue using neomycin sulfate solutions will direct the pharmacist to grind neomycin sulfate tablets or to further dilute neomycin sulfate oral solution. The comments argued that this would risk exposing the patient to potentially adverse ingredients because the pure bulk neomycin sulfate powder and the sterile injection would no longer be used. Another comment asserted that neomycin sulfate tablets are not a good substitute for the bulk powder because, in addition to being inconvenient, the binders in the tablets do not dissolve. The resulting solution would be cloudy and would have a residue. In addition, the use of tablets or solution will make it more difficult and time-consuming for the pharmacist to make the compounded solution.

Many comments said that the withdrawal from the market of neomycin sulfate for prescription compounding would result in increased medical costs to practitioners and patients. The comments said other forms of neomycin sulfate, such as the oral solution, the tablet form, and other

products which have neomycin sulfate as a component, will be used for prescription compounding instead of the bulk powder. The comments cited data to demonstrate the higher costs of these neomycin sulfate products and other aminoglycosides.

FDA must protect the public against the risks of death, disability due to irreversible bilateral deafness, renal failure, and respiratory paralysis associated with unapproved uses of neomycin sulfate. The agency cannot support the continued misuse of the product on the basis of cost or convenience.

Rather than removing the product from the market as originally proposed, FDA is revising the regulations and requiring labeling that will contain strong warnings about the unapproved uses. FDA is hopeful that these measures will help to prevent further misuse of neomycin sulfate.

25. Several comments asserted that FDA's proposal to request a recall to the retail level for all products covered by certificates for batches of neomycin sulfate for prescription compounding is excessive and unnecessary. The comments stated that the publicity received by the proposal has already alerted most users to the potential hazards of unapproved uses of the product. The comments also stated that recall or discontinuing certification penalizes those who are using the product for indications that FDA considers acceptable. The comments also questioned FDA's urgency in requesting a recall, noting that the agency waited 27 months to publish the proposal and that many more months will elapse before the final rule is published.

The agency agrees that a recall may no longer be necessary because the final rule imposes only a new requirement for drug labeling rather than revocation of certification, as proposed. Nevertheless, it is important that prescribers and pharmacists be informed about the risks of toxicity associated with the uses of neomycin sulfate that result in significant systemic absorption. Therefore, supplements providing for package insert labeling in accordance with the guideline must be submitted to approved antibiotic applications or abbreviated antibiotic applications for the products affected by this final rule, by June 14, 1988.

26. One comment stated the proposal would contribute to the elimination of the small pharmaceutical company from the marketplace because it is the smaller company that usually manufactures and sells bulk products, while the larger pharmaceutical manufacturers sell dosage form medications.

FDA disagrees. This final action is not removing the product from the marketplace and thus is not contributing to the elimination of any pharmaceutical companies, small or large.

27. One comment stated that it was not included in early FDA meetings with The Upjohn Co. and Elkins-Sinn, Inc., two firms that marketed neomycin sulfate for prescription compounding. The comment said it was not aware of FDA's intention to withdraw the product from the market until August 11, 1979, whereas the other firms knew as early as 1977.

FDA did not hold early meetings with pharmaceutical manufacturers as contended by the comment. The issue of neomycin sulfate was discussed at an open meeting of FDA's Anti-Infective Agents Advisory Committee on April 4, 1977. A representative from Squibb & Sons, Inc., attended the meeting and participated in the discussion. Although the meeting was announced in advance in the **Federal Register** and open to the public, no other pharmaceutical manufacturer chose to participate. Both the minutes of the meeting and the transcript of the proceedings are filed with FDA's Dockets Management Branch and are available for public inspection.

28. One comment claimed the proposal is based largely on information obtained from an unnamed pharmaceutical company. The comment stated that no written documentation or information is contained in the proposal to substantiate the company's position, and the simple fact that this unnamed company received 100 inquiries concerning neomycin sulfate does not mean that the drug is not safe or effective. The comment said it is possible that the unnamed company has economic motives for its position.

The proposal was not based on information from a pharmaceutical company. FDA's position is documented by publications in the medical literature cited in this document and by FDA's drug experience files, and is supported by both the Anti-Infective Agents Advisory Committee's recommendations and by the Drug Efficacy Study Implementation project.

IV. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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V. Conclusions

FDA has reached two conclusions as a result of reviewing (1) the written and oral comments on the proposal, (2) findings of the Drug Efficacy Study Implementation published in the **Federal Register** of May 13, 1970 (35 FR 7464) and February 29, 1972 (37 FR 4224), (3) reports in the medical literature, (4) reports in the agency's drug experience files, and (5) information available to support updating currently approved neomycin products. First, there are inadequate data to support the safety and efficacy of neomycin sulfate for use in irrigation solutions in the treatment of infected wounds and ulcers; for use on burns; for prophylactic local use before, during, or after surgical procedures, e.g., intraperitoneal suction-irrigation, fractures and joint replacement surgery, neurosurgery, and for other types of surgery and traumatic wounds; for rectal or colonic irrigation or as a retention enema; for intrapleural instillations; for use in wet dressings; for aerosol inhalation; for solutions to soak bone grafts, skin grafts, and silastic implants; and for any similar use under conditions where neomycin may be systemically absorbed in significant quantities. In addition to the lack of evidence of safety and efficacy of neomycin sulfate for these indications, there is evidence of significant drug toxicity for most of them.

Second, the agency finds that there is adequate safety and efficacy information to continue to allow marketing of nonsterile neomycin sulfate for compounding oral prescription products if full prescribing information is provided.

VI. Amendment to the Antibiotic Regulations

Under 21 CFR Part 433.1 (a) and (b), antibiotic drugs are exempt from batch certification requirements if: (1) The drug is approved for marketing under an appropriate antibiotic application or abbreviated antibiotic application, (2) the drug is packaged and labeled for dispensing in accordance with the applicable regulation or approved application, (3) the bulk drug used in preparing the antibiotic drug product meets the standards of identity, strength, quality, and purity specified in the applicable regulation or approved application, and (4) the antibiotic drug product meets the standards of identity, strength, quality, and purity specified in the applicable regulation or approved application.

The regulation applicable to nonsterile neomycin sulfate for prescription compounding (21 CFR 444.942a), is being amended to change the product name to specify use in compounding oral products and to require package insert labeling. With these amendments, nonsterile neomycin sulfate for prescription compounding cannot be certified or released. Except where other labeling has been approved in an applicable application, nonsterile neomycin sulfate for prescription compounding is not exempt from batch certification requirements. Only nonsterile neomycin sulfate products that are named and labeled in accordance with the amended regulations will be exempt from batch certification.

VII. Economic and Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This final rule does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12291 does not apply to an action such as this at the stage where the action is subject to opportunity for hearing under 5 U.S.C. 556 and 557. Furthermore, the Regulatory Flexibility Act does not apply to this proceeding because the proposed rule was issued before the effective date of the Act. Nevertheless, the agency has examined the economic impact of this final rule and has determined that this impact is insignificant. The final rule amends the antibiotic regulations to change the product name and to require package insert labeling. No additional burdens are imposed upon manufacturers.

VIII. Availability of Guideline

A separate notice published elsewhere in this issue of the **Federal Register** announces the availability of guideline labeling that describes the kind of information to be included in the package insert labeling for this product. The guideline sets forth specific language that would be acceptable to the agency. Copies are available from Dockets Management Branch (address above) under Docket No. 87D–0315.

IX. Notice of Opportunity for a Hearing

The amendments become effective 60 days after the date of publication of this final rule. At that time, batches of nonsterile neomycin sulfate will no longer be certified, released, or exempt from certification unless named and labeled in accordance with the amended regulations. Any person who will be adversely affected by the final rule amending the antibiotic regulations may file objections to it and request a hearing as provided in section 507(f) of the act (21 U.S.C. 357). Reasonable grounds for the hearing must be shown, as specified in 21 CFR 314.300. If requests for hearing are granted both on objections to the final rule and on the proposal to withdraw approval of the antibiotic regulations that is published elsewhere in this issue of the **Federal Register**, the hearings will be combined in a single proceeding under 21 CFR Part 12 and 5 U.S.C. 556 and 557.

Any person subject to this final rule who decides to seek a hearing shall file: (1) on or before May 16, 1988, a written notice of participation and request for hearing, and (2) on or before June 14, 1988, the data, information, and analyses on which the person relies on to justify a hearing, as specified in 21 CFR 314.300. Any other interested person may also submit comments. The procedures and requirements governing this notice of opportunity for hearing, a notice of participation and request for hearing, a submission of data, information, and analyses to justify a hearing, or other comments, and a grant or denial of a hearing are contained in § 314.300.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that no genuine and substantial issue of fact precludes the action taken by this order,

or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request the hearing, making findings and conclusions and denying a hearing.

All submissions under this order are to be filed in three copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 444

Antibiotics.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 444 is amended as follows:

PART 44—OLIGOSACCHARIDE ANTIBIOTIC DRUGS

1. The authority citation for 21 CFR Part 444 continues to read as follows:

Authority: Sec. 507, 59 Stat. 463 as amended (21 U.S.C. 357); 21 CFR 5.10.

2. Section 444.942a is amended by revising the section heading and by revising paragraphs (a)(1) introductory text, (3) introductory text, and (4)(i), to read as follows:

§ 444.942a Neomycin sulfate for compounding oral products.

(a) * * *

(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate for compounding oral products is the sulfate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

* * * * *

(3) *Labeling.* It shall be labeled in accordance with the requirements prescribed by § 432.5(a) of this chapter. Its expiration date is 12 months.

(4) * * *

(i) In addition to complying with the conditions of § 431.1 of this chapter, a person who requests certification of a batch of neomycin sulfate for compounding oral products shall submit with the request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by results of tests and assays made on the batch for potency, moisture, pH, and identity.

* * * * *

Dated: March 30, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88-8189 Filed 4-14-88; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 444

[Docket No. 79N-0151]

Oligosaccharide Antibiotic Drugs; Sterile Neomycin Sulfate

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the antibiotic drug regulations to revoke the provisions for certification of neomycin sulfate in sterile vials for parenteral use. This action is being taken because the risks involved in the parenteral use of neomycin sulfate are judged to outweigh any benefits that might be derived from its continued availability. FDA is offering an opportunity for a hearing on objections to this revocation under the formal rulemaking provisions in section 507(f) of the Federal Food, Drug, and Cosmetic Act (the act) and the Administrative Procedure Act (5 U.S.C. 556 and 557). Elsewhere in this issue of the **Federal Register** is a notice offering an opportunity for a hearing on the proposal to withdraw the approval of antibiotic applications and abbreviated antibiotic applications for neomycin sulfate in sterile vials for parenteral use.

DATES: Effective June 14, 1988; comments, notices of participation, and requests for hearing by May 16, 1988; data, information, and analyses to justify a hearing by June 14, 1988.

ADDRESSES: Written comments concerning requests for hearing, supporting data, and information to Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this final rule to a specific product to Division of Drug Labeling Compliance (HFN-310), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judy O'Neal, Center for Drug Evaluation and Research (HFN-366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8041.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 27, 1979 (44 FR 44180), FDA proposed to revoke the provisions of its antibiotic drug regulations (21 CFR 444.42a) that provide for the certification of neomycin sulfate in sterile vials for parenteral use. This action was taken because there is clinical evidence that parenterally administered neomycin sulfate can induce significant toxicity including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade. In addition, there is evidence that the sterile vial of neomycin sulfate, which has been approved by FDA only for intramuscular administration in the treatment of certain urinary tract infections, is being used to prepare irrigation solutions. As concluded in the Drug Efficacy Study Implementation notice published on February 29, 1972 (37 FR 4224), evidence of effectiveness is lacking for the use of sterile neomycin sulfate in the irrigation of wounds. Moreover, there is clinical evidence that such use poses a significant risk to the patient, as described in the July 27, 1979, proposal and in another final rule published elsewhere in this issue of the **Federal Register** concerning neomycin sulfate for prescription compounding. A third reason for the proposed action was that, as concluded by FDA's Anti-Infective Agents Advisory Committee, use of this dosage form for the single remaining approved indication, the treatment of urinary tract infection, is no longer acceptable because of the availability of newer, safer antibiotics that are as effective as, or more effective than, parenteral neomycin sulfate and that do not present comparable risks.

After the proposal regarding sterile neomycin sulfate was published on July 27, 1979, FDA received three requests for an informal conference, and also received two requests for an extension of the comment period on the related proposal regarding nonsterile neomycin sulfate for prescription compounding. A notice of opportunity for an informal conference was published in the **Federal Register** of October 19, 1979 (44 FR 60331), and an informal conference was held on November 20, 1979. In addition, the comment period was extended for 30 days after the date of the informal conference.

The agency has carefully considered all of the comments received on the proposal and has concluded that the risks involved in the parenteral use of neomycin sulfate outweigh any benefits that might be derived from such use. This final rule amends the regulations to

APPENDIX 11:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 87D-0315]

Oligosaccharide Antibiotic Drugs; Neomycin Sulfate for Prescription Compounding; Opportunity for Hearing on Proposal To Withdraw Approval of Applications; Availability of Guideline Labeling

AGENCY: Food and Drug Administration.

ACTION: Notice of opportunity for hearing and availability of guideline labeling.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of guideline labeling for neomycin sulfate for compounding oral products (formerly neomycin sulfate for prescription compounding) and is also offering an opportunity for a hearing on the proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for nonsterile neomycin sulfate products that are not labeled in accordance with the antibiotic regulations. In a final rule published elsewhere in this issue of the **Federal Register**, FDA is revising the regulations to change the product name and to require package insert labeling that informs users of the product about the risks associated with neomycin sulfate and recommends the product for oral use only. These actions are being taken because nonsterile neomycin sulfate, a prescription drug with a recognized potential for producing toxicity, is now supplied for prescription compounding without adequate labeling. The drug is being used for indications for which it lacks evidence of effectiveness and for which there is clinical evidence of significant risk to the patient. FDA is offering an opportunity for a hearing on the proposal to withdraw approval of the applications under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)).

DATES: Guideline labeling available April 15, 1988. Supplements providing for package insert labeling to be submitted by June 14, 1988; notice of participation and request for hearing by May 16, 1988; data, information, and analyses to justify a hearing by June 14, 1988.

ADDRESSES: Written comments and requests for single copies of the guideline labeling, requests for hearing, and supporting data and information to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. (Send two self-addressed adhesive labels to assist the Branch in processing your requests.)

Requests for opinion of the applicability of this notice to a specific product to Division of Drug Labeling Compliance (HFN-310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Judy O'Neal, Center for Drug Evaluation and Research (HFN-366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8041.

SUPPLEMENTARY INFORMATION: In a final rule published elsewhere in this issue of the **Federal Register**, FDA is amending the antibiotic drug regulations (specifically, 21 CFR 444.942a) that provide for the certification of nonsterile neomycin sulfate for prescription compounding. As described in the final rule, there are inadequate data to support the safety and efficacy of neomycin sulfate for use in irrigation solutions in the treatment of infected wounds and ulcers; for use on burns; for prophylactic local use before, during, or after surgical procedures, e.g., intraperitoneal suction-irrigation, fractures and joint replacement surgery, neurosurgery, and for other types of surgery and traumatic wounds; for rectal or colonic irrigation or as a retention enema; for intrapleural instillations; for use in wet dressings; for aerosol inhalation; for solutions to soak bone grafts, skin grafts, and silastic implants; and for any similar use under conditions where neomycin may be systemically absorbed in significant quantities. In addition to the lack of evidence of safety and efficacy of neomycin sulfate for these indications, there is evidence of significant drug toxicity for most of them.

FDA finds, however, that there is adequate safety and efficacy information to continue to allow marketing of nonsterile neomycin sulfate for compounding oral prescription products if full prescribing information is provided. Therefore, FDA is amending the antibiotic drug regulations to change the product name from "neomycin sulfate for prescription compounding" to "neomycin sulfate for compounding oral products" and to require labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use. The labeling will state that the product is recommended for oral use only. As discussed later, FDA is announcing the availability of guideline labeling for neomycin sulfate for compounding oral products under Docket No. 87D-0315.

However, amending the antibiotic regulations is not sufficient to accomplish the desired action. The drug products affected by this notice were being certified until the antibiotic drug regulations were amended to exempt antibiotic-containing drugs from batch certification requirements (47 FR 39155; September 7, 1982). Under the new regulations specifying the conditions of the exemption, an antibiotic drug must be packaged and labeled in accordance with the applicable regulations except where FDA has approved other labeling in an antibiotic application. Therefore, in addition to revising the applicable regulations, it is necessary to withdraw approval of antibiotic applications that provide for other labeling.

An antibiotic drug exempt from certification requirements under 21 CFR 433.1(b) is subject, following its approval, to section 505 of the act and applicable parts of the new drug regulations (21 CFR Parts 310 through 314 and 433.1(c)). This notice proposes to withdraw approval, under section 505(e) of the act, of the antibiotic applications and abbreviated antibiotic applications that are not supplemented, within 60 days of the effective date of the final rule, to provide for the new product name and package insert labeling. The agency has prepared guideline labeling that manufacturers and suppliers may adopt to ensure that their labeling complies with the requirements of the revised regulations.

The products known by FDA to be subject to this notice are:

1. No. 61-043, held by the Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
2. No. 61-085, held by Pfizer, Inc., 235 East 42nd St., New York, NY 10017.
3. No. 61-169, held by S. B. Penick and Co., 540 New York Ave., Lyndhurst, NJ 07071.
4. No. 61-579, held by Pharma-Tek, Inc., P.O. Box AB, Huntington, NY 11743.
5. No. 61-698, held by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.
6. No. 62-385, held by Paddock Laboratories, Inc., 3101 Louisiana Ave. North, Minneapolis, MN 55421.

On the basis of all the data and information available, the Center for Drug Evaluation and Research finds that nonsterile neomycin sulfate is unsafe for use except when named "Neomycin Sulfate for Compounding Oral Products" and used in accordance with appropriate package insert labeling.

Therefore, notice is given to the holders of the antibiotic applications listed above, and to all other interested

persons, that the Center for Drug Evaluation and Research proposes to issue an order under section 505(e) of the act, withdrawing approval of the antibiotic applications and all amendments and supplements thereto, unless supplements providing for a change in the product name and addition of package insert labeling in accordance with 21 CFR 444.942a of the regulations are submitted by June 14, 1988. This notice is based on the ground that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the applications were approved. With the withdrawal of approval of the applications identified above, shipment in interstate commerce of nonsterile neomycin sulfate that is not certified, released, or exempt from certification will be unlawful.

In accordance with section 505 of the act and the regulations promulgated under this section (21 CFR Parts 310 and 314), the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to the drug product named above (21 CFR 310.6) and that is not the subject of an antibiotic application are hereby given an opportunity for a hearing to show why approval of the application should not be withdrawn, and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug product named above and of all identical, related, or similar drug products not the subject of an approved application. If requests for hearing are granted both on objections to the final rule published elsewhere in this issue of the **Federal Register** and on withdrawal of approval of the antibiotic applications, the hearings will be combined in a single proceeding under 21 CFR Part 12 and 5 U.S.C. 556 and 557.

In addition to the holders of the applications specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved antibiotic application, that is identical, related, or similar to the drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he or she manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product that may be identical, related, or similar to a drug product named in this notice by writing to the Division of Drug Labeling Compliance (address above).

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act (21 U.S.C. 321(p)), or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

The applicant or any other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file: (1) on or before May 16, 1988, a written notice of participation and request for hearing, and (2) on or before June 14, 1988, the data, information, and analyses on which the person relies on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments. The procedures and requirements governing this notice of opportunity for hearing, a notice of participation and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of participation and request for hearing, as required by 21 CFR 314.200, constitutes an election by the person not to make use of the opportunity for a hearing concerning the action and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and FDA will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses; the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request the hearing, making findings and conclusions and denying a hearing.

All submissions under this notice are to be filed in three copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

The guideline labeling is issued under § 10.90 (b) (21 CFR 10.90(b)), which provides for the use of guidelines to establish procedures of general applicability that are not legal requirements, but are acceptable to the agency. A person who follows this guideline is assured that his or her conduct is acceptable to the agency. The agency advises that the labeling guideline for neomycin sulfate for compounding oral products complies with the prescription drug labeling regulations in §§ 201.56, 201.57, and 201.100 and can be relied upon by any person to meet these requirements. Under the provisions of § 314.70 (c) (21 CFR 314.70(c)), the guideline labeling may be used before approval of a supplement to a new drug application. A person may choose to use alternative labeling statements that are not provided in the guideline. If a person chooses to depart from the guideline, he or she may discuss the matter further with the agency to prevent expenditure of money and effort for labeling that the agency may later determine to be unacceptable.

Effective April 15, 1988, a person may adopt the labeling guideline to comply with labeling requirements for neomycin sulfate for compounding oral products. Interested persons may submit written comments on the guideline to the Dockets Management Branch (address above). Comments should be in three copies, identified with Docket No. 87D-0315. The guideline and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. If, as a result of comments received on the guideline labeling, FDA determines that the labeling should be revised, a notice will be published in the **Federal Register** announcing that such changes have been made.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 507, 52 Stat. 1050–1053 as amended (21 U.S.C. 352, 355) and 59 Stat. 463 as amended (21 U.S.C. 357)) and under authority delegated to the Center for Drug Evaluation and Research (21 CFR 5.70, 5.78, and 5.82).

APPENDIX 12:

Finance Company, Plano, Illinois, and thereby engage in making and servicing loans pursuant to § 225.25(b)(1) of the Board's Regulation Y, and in the sale of insurance relating directly to the extensions of credit pursuant to § 225.25(b)(8) of the Board's Regulation Y.

B. **Federal Reserve Bank of Kansas City** (Thomas M. Hoenig, Vice President) 925 Grand Avenue, Kansas City, Missouri 64198:

1. *IntraOklahoma Bancshares, Inc.*, Ponca City, Oklahoma; to acquire Strategic Data Services, Ltd. (SDSL), a limited partnership, and Strategic Data Services, Inc. (SDSI), a general partner of SDSL, and thereby engage in providing data processing and transmission services pursuant to § 225.25(b)(7) of the Board's Regulation Y, through a joint-venture arrangement with The First National Bank and Trust Company of Ponca City, Oklahoma.

Board of Governors of the Federal Reserve System, November 30, 1988.

James McAfee,

Associate Secretary of the Board.

[FR Doc. 88-27987 Filed 12-5-88; 8:45 am]

BILLING CODE 6210-01-M

Wells Fargo & Co.; Proposed Acquisition of Savings and Loan Association

Wells Fargo & Company ("Wells Fargo"), San Francisco, California, has applied under § 225.23(a)(3) of the Board's Regulation Y (12 CFR 225.23(a)(3)) for the Board's approval under section 4(c)(8) of the Bank Holding Company Act (12 U.S.C. 1843(c)(8)) and § 225.21(1) of Regulation Y (12 CFR 225.21(a)) to acquire 100 percent of the voting shares of Perpetual Savings Association ("Perpetual"), Santa Ana, California, which are to be issued after the conversion of Perpetual from a mutual thrift institution to a stock federal savings bank.

The Board previously has determined by order that the operation of a thrift institution (including a savings and loan association) is closely related to banking, but not, as a general matter, a proper incident to banking under section 4(c)(8) of the Act. *See, e.g., Citicorp*, 72 Federal Reserve Bulletin 724 (1986). However, the Board has approved several proposals involving the acquisition of failing thrift institutions on the basis that any adverse effects would be overcome by the public benefits of preserving the failing thrift institutions. *Citicorp, supra; The Chase Manhattan Corporation*, 71 Federal Reserve Bulletin 462 (1985).

Interested persons may express their views in writing on the question whether consummation of the proposed acquisition can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interest or unsound banking practices." Any comments must conform with the requirements of the Board's Rules of Procedure (12 CFR 262.3(e)).

Comments regarding this application must be submitted in writing and must be received at the offices of William W. Wiles, Secretary, Board of Governors of the Federal Reserve System, Room 2222, Eccles Building, 20th Street and Constitution Avenue NW., Washington, DC 20551, not later than 5:00 p.m. on Tuesday, December 20, 1988. This application is available for immediate inspection at the offices of the Board of Governors and the Federal Reserve Bank of San Francisco.

Board of Governors of the Federal Reserve System, December 2, 1988.

James McAfee,

Associate Secretary of the Board.

[FR Doc. 88-28111 Filed 12-5-88; 8:45 am]

BILLING CODE 6210-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Secretary's Commission on Nursing; Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463), announcement is made of the following national advisory body scheduled to meet during the month of October 1988:

Name: Secretary's Commission on Nursing.

Date: Monday, December 12, 1988.

Time: 11:00 a.m.

Place: Room 800, Hubert H. Humphrey Building, 200 Independence Avenue SW., Washington, DC.

Purpose: The Secretary's Commission on Nursing will advise the Secretary of Health and Human Services on how the public and private sectors can work together to address problems and implement solutions regarding the supply of active registered nurses. The Commission will consider the recruitment and retention of nurses in the U.S. Public Health Service, the Veterans Administration and the Department of Defense. As appropriate for its work, the Commission will consider the findings of studies which are relevant to the development of a multi-year action plan for implementation by the public and private sectors.

The agenda for the December 12 meeting will consist of discussion about steps that can be taken to encourage private and public sector organizations to implement the Commission's recommendations and proposed strategies. In addition, the Secretary of the Department of Health and Human Services will be presented with the Commission's report and given an overview of its contents.

Agenda items are subject to change as priorities dictate.

Anyone wishing to attend these meetings who is hearing impaired and requires the services of an interpreter for the deaf should contact the Commission one week before the schedule meeting. All such requests, as well as requests for information, should be addressed to the Secretary's Commission on Nursing, Hubert H. Humphrey Building, Room 600E, 200 Independence Avenue SW., Washington, DC, 20201, telephone 202/245-0409.

Lillian K. Gibbons,

Executive Director, Secretary's Commission on Nursing.

[FR Doc. 88-28153 Filed 12-5-88; 8:45 am]

BILLING CODE 4150-04-M

Food and Drug Administration

[Docket No. 87D-0315]

Oligosaccharide Antibiotic Drugs; Neomycin Sulfate for Prescription Compounding; Withdrawal of Approval of Abbreviated Antibiotic Drug Applications

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of five abbreviated antibiotic drug applications (AADA's) for neomycin sulfate for prescription compounding. AADA 61-579, held by Pharma-Tek, Inc., is not affected by this notice because a hearing requested by the firm is currently under consideration. This withdrawal action is being taken because these products are being used for indications for which they lack evidence of safety and effectiveness, and for which there is clinical evidence of significant risk to the patient.

EFFECTIVE DATE: January 5, 1989.

FOR FURTHER INFORMATION CONTACT: Margaret F. Sharkey, Center for Drug Evaluation and Research (HFD–366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8041.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of April 15, 1988 (53 FR 12662), the Director of the Center for Drug Evaluation and Research offered an opportunity for a hearing on a proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for nonsterile neomycin sulfate for prescription compounding not labeled in accordance with applicable amended antibiotic regulations (21 CFR 444.942a). In the same issue (53 FR 12644), FDA amended the regulations governing these products and offered a labeling guideline because the drug was being used for indications for which it lacked evidence of safety and effectiveness, and for which there was clinical evidence of significant risk to the patient. The final rule became effective on June 14, 1988.

The amendments to 21 CFR 444.942a changed the product name from "neomycin sulfate for prescription compounding" to "neomycin sulfate for compounding oral products" and required product labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use.

Manufacturers and suppliers were notified that they would have to supplement their applications within 60 days of the effective date of the final rule to provide for the new product name and package insert labeling. Alternatively, a manufacturer or supplier could request a hearing. No supplements were submitted for any of the applications. One supplier, Pharma-Tek, Inc., requested a hearing.

The sponsors of the five products listed below failed to file a request for a hearing and did not supplement their applications. Accordingly, FDA is withdrawing approval of the following AADA's:

1. AADA 61–043; held by The Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
2. AADA 61–805; held by Pfizer, Inc., 235 East 42nd St., New York, NY 10017.
3. AADA 61–169; held by S.B. Penick and Co., 540 New York Ave., Lyndhurst, NJ 07071.
4. AADA 61–698; held by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.
5. AADA 62–385; held by Paddock Laboratories, Inc., 3101 Louisiana Ave. North, Minneapolis, MN 55421.

The Director of the Center for Drug Evaluation and Research, under the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052–1053 as amended (21 U.S.C. 355(e))) and under authority delegated to him (21 CFR 5.82), finds that clinical or other experience, tests, or other scientific data show that the drug products listed above are unsafe for use under the conditions of use upon basis for which their applications were approved. Therefore, pursuant to the foregoing finding, approval of the AADA's listed above is hereby withdrawn effective January 5, 1989. Shipment in interstate commerce of the products listed above will then be unlawful.

This notice does not apply to AADA 61–579, held by Pharma-Tek, Inc., P.O. Box AB, Huntington, NY 11743. The product covered by AADA 61–579 is the subject to a pending hearing request and will be the subject of a future **Federal Register** announcement.

Dated: November 28, 1988.

Carl C. Peck,

Director, Center for Drug Evaluation and Research.

[FR Doc. 88–28027 Filed 12–5–88; 8:45 am]
BILLING CODE 4160–01–M

[Docket No. 79N–0151]

Oligosaccharide Antibiotic Drugs; Neomycin Sulfate for Injection; Withdrawal of Approval of Abbreviated Antibiotic Drug Applications

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of four abbreviated antibiotic drug applications (AADA's) for neomycin sulfate in sterile vials for injection. This withdrawal action is being taken because the risks involved in the parenteral use of neomycin sulfate are judged to outweigh any benefits that may be derived from its continued availability.

EFFECTIVE DATE: January 5, 1989.

FOR FURTHER INFORMATION CONTACT: Margaret F. Sharkey, Center for Drug Evaluation and Research (HFD–366), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8041.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of April 15, 1988 (53 FR 12664), the Director of the Center for Drug Evaluation and Research offered an opportunity for a hearing on a proposal to withdraw approval of antibiotic applications and abbreviated antibiotic applications for neomycin sulfate in sterile vials for parenteral use. FDA also amended the antibiotic regulations for sterile neomycin sulfate (21 CFR 444.42a) by deleting all provisions for the injectable dosage form so that neomycin sulfate packaged in sterile vials for dispensing could not be certified or released (see 53 FR 12658; April 15, 1988). These actions were deemed necessary because of the toxicity associated with the unapproved use of this drug in the irrigation of wounds. In addition, the Director concluded that the use of this dosage form for the single remaining approved indication, the treatment of urinary tract infection, is no longer acceptable because of the availability of newer, safer antibiotics that are as effective as, or more effective than, parenteral neomycin sulfate and that do not present comparable risks.

In response to the April 15, 1988, **Federal Register** notice, no holders of approved applications requested a hearing. Accordingly, FDA is withdrawing approval of the following applications:

1. AADA 60–366, Neomycin Sulfate for Injection, U.S.P., held by E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540.
2. AADA 60–477, Mycifradin Injectable, held by The Upjohn Co., Kalamazoo, MI 49001.
3. AADA 61–084, Neomycin Sulfate for Injection, held by Pfizer Inc., 235 East 42nd St., New York, NY 10017.
4. AADA 61–198, Neomycin Sulfate for Injection, U.S.P., held by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034.

The Director of the Center for Drug Evaluation and Research, under the Federal Food, Drug and Cosmetic Act (sec. 505(e), 52 Stat. 1052–1053 as amended (21 U.S.C. 355(e))) and under authority delegated to him (21 CFR 5.82), finds that clinical or other experience, tests, or other scientific data show that the drug products listed above are unsafe for use under the conditions of use upon the basis for which their applications were approved. Therefore, pursuant to the foregoing finding, approval of the AADA's listed above is hereby withdrawn effective January 5, 1989. Shipment in the interstate commerce of the products listed above will then be unlawful.

APPENDIX 13:

(2) If no paint contamination is detected on the actuator pistons and the moisture indicator of the trim actuator is pink or white, prior to further flight, replace the trim actuator with a new or serviceable trim actuator and either replace or regenerate the desiccant in accordance with the alert service bulletin.

(3) If any paint contamination is detected on the actuator pistons, prior to further flight, remove the paint in accordance with the alert service bulletin.

Note 2: Aviac Technologies, the manufacturer of the desiccant, has issued Identification Procedure for Desiccant DAV/AP98–214, Revision 0, dated April 22, 1998, as an additional source of service information to determine the level of saturation of the desiccant.

(b) Within 2 months after the effective date of this AD, perform a one-time visual inspection to verify installation of the flat gasket in each end of the flex drive, and to determine if the flat gasket is in good condition (i.e., shows no signs of wear), in accordance with Dornier Alert Service Bulletin ASB–328–27–017, Revision 2, dated July 28, 1998.

(1) If the gasket is installed and in good condition, no further action is required by paragraph (b) of this AD.

(2) If the gasket is missing or is installed and not in good condition, prior to further flight, replace the gasket with a new gasket, and torque the nuts, in accordance with the alert service bulletin.

Note 3: Accomplishment of the actions required by paragraphs (a) and (b) of this AD, prior to the effective date of this AD, in accordance with Dornier Alert Service Bulletin ASB–328–27–017, Revision 1, dated October 1, 1997, is considered acceptable for compliance with the applicable actions specified in paragraphs (a) and (b) of this AD.

(c) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 4: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

(d) Special flight permits may be issued in accordance with §§ 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 5: The subject of this AD is addressed in German airworthiness directive 97–188, dated July 3, 1997.

Issued in Renton, Washington, on October 1, 1998.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98–26964 Filed 10–7–98; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N–0655]

List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to include a list of drug products that may not be used for pharmacy compounding pursuant to the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

DATES: Comments must be received on or before November 23, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Modernization Act (Pub. L. 105–115) into law on November 21, 1997. One of the issues addressed in this new legislation is the applicability of the act to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized medication for an individual patient. Section 127 of the Modernization Act, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). Section 127(b) of the Modernization Act provides that section 503A of the act will become effective on November 21, 1998, 1 year from the date of the Modernization Act's enactment.

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions under section 503A. One of the conditions is that the licensed pharmacist or licensed physician does not ''compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.''

II. Rulemaking to Establish the List

In accordance with section 503A of the act, FDA has developed a list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. Many of the drug products on the list were withdrawn from the market through official proceedings, including publication of a notice in the **Federal Register**. For these drug products, this preamble to the proposed rule includes the reason for the withdrawal and the citation to the official notice of withdrawal. Other products, both approved and unapproved, were removed from the market voluntarily by the manufacturer or application holder, and FDA has information indicating that the reason for the removal was because the product was unsafe or not effective. In such cases, the reason for the removal is provided, and additional sources of information on the drug can be found in the docket identified by the number found in brackets in the heading of this document.

This proposed rule is the first of a series of rulemaking proceedings to establish the list of withdrawn or removed drug products, as the development and issuance of this list will be an ongoing process. The primary focus of this proposed rule is drug products that have been removed or withdrawn for safety reasons. FDA intends that future rulemaking

proceedings will focus on drug products that were withdrawn for reasons of effectiveness, on drug products that are identified as having been withdrawn for reasons of safety or effectiveness after the preparation of this proposed rule, and on additional drug products that will be proposed for inclusion on the list either during the comment period or subsequently.

FDA is specifically seeking comment on whether additional drug products should be added to the list and whether products now on the list should remain on the list. Persons submitting comments recommending that a drug product be added to the list should include appropriate documentation, including any notices published in the **Federal Register**. In addition, individuals and organizations may petition FDA to amend the list at any time through the regular citizen petition process described in 21 CFR 10.30.

After evaluating the comments on this proposed rule and consulting an advisory committee on compounding, as required by section 503A(d)(1) of the act, FDA will issue the list as a final rule which will be codified in the Code of Federal Regulations. The initial list published as a final rule may include all or some of the products proposed for inclusion on the list in this proposal, depending upon the comments received. Additional products will be added to the list through the rulemaking process after the data on the products are evaluated, and after consultation with the advisory committee on compounding.

III. Description of the Proposed Rule

FDA is proposing that the drug products described in this section be included in the list of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. Compounding a drug product that appears on this list is not covered by the exemption provided in section 503A(a) of the act, and may be subject to enforcement action under sections 501(a)(2)(B), 502(f)(1), and 505 (among other applicable provisions) of the act.

The listings are arranged alphabetically by the established name of the active ingredient contained in the drug product. For many of the drugs, the proprietary or trade name of some or all of the drug products which contained the active ingredient are also given in the preamble paragraphs describing the withdrawn or removed drug products. Some of the drugs listed were withdrawn or removed from the market based on problems relating only to one dosage form or route of administration. In such cases, the listing for that drug product reflects that fact, e.g., ''*Neomycin Sulfate*: Parenteral drug products containing neomycin sulfate.'' In other cases, the problem is associated with the active ingredient, or appears to relate to other dosage forms or routes of administration, and the listing reflects that fact, e.g., ''*Adrenal Cortex*: All drug products containing adrenal cortex.'' In several instances, a particular formulation, dosage form, or route of administration is explicitly excluded from an entry on the list because there is an approved drug (that has not been withdrawn or removed from the market) that contains the same active ingredient(s) as the drug product that has been withdrawn or removed from the market. In these instances, the listing includes the appropriate qualification, e.g., ''*Suprofen*: All drug products containing suprofen (except ophthalmic solutions).''

In several cases, the withdrawn drug products are identified according to the established name of the active ingredient, listed as a particular salt or ester of the active moiety, e.g., ''*Dexfenfluramine hydrochloride*: All drug products containing dexfenfluramine hydrochloride.'' Although the specific listing may be limited to a particular salt or ester, other salts or esters of the active moiety will not qualify for the compounding exemptions in section 503A of the act unless (among other requirements) the particular salt or ester is the subject of a United States Pharmacopeia or National Formulary monograph; is a component of an FDA approved drug; or appears on the FDA list of bulk drug substances that may be used for compounding. (See section 503A(b)(1)(A)(i) of the act).

The list is being proposed as § 216.24 of Title 21 of the Code of Federal Regulations. This new section will be included in a new part, part 216, which is currently intended to include all FDA regulations whose primary purpose is implementation of the pharmacy compounding provisions found in section 503A of the act.

The following drug products are proposed for inclusion in proposed § 216.24. The supporting documentation for each listed drug product may be found in the docket identified by the number found in brackets in the heading of this document. The supporting documentation will be arranged alphabetically according to the established name of the active ingredient of the drug products.

Adenosine phosphate: All drug products containing adenosine phosphate. Adenosine phosphate, formerly marketed as a component of Adeno for injection, Adco for injection, and other drug products, was determined to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. FDA directed the removal of these drug products from the market in 1973.

Adrenal cortex: All drug products containing adrenal cortex. The low level of corticosteroids found in adrenal cortex injection and adrenal cortex extract were determined to present a substantial risk of undertreatment of serious conditions, such as adrenal cortical insufficiency, burns, and hypoglycemia. FDA determined that adrenal cortex for injection and adrenal cortex extract presented a significant potential hazard and directed the removal of these drug products from the market in January 1978.

Azaribine: All drug products containing azaribine. The use of azaribine, formerly marketed as Triazure tablets, was associated with very serious thromboembolic events. Approval of the new drug application (NDA) for Triazure tablets was withdrawn June 10, 1977 (see the **Federal Register** of June 10, 1977 (42 FR 29998)).

Benoxaprofen: All drug products containing benoxaprofen. The use of benoxaprofen, formerly marketed as Oraflex tablets, was associated with fatal cholestatic jaundice among other serious adverse reactions. The holder of the approved application voluntarily withdrew Oraflex tablets from the market on August 5, 1982.

Bithionol: All drug products containing bithionol. Bithionol, formerly marketed as an active ingredient in various topical drug products, was shown to be a potent photosensitizer with the potential to cause serious skin disorders. Approvals of the NDA's for bithionol drug products were withdrawn on October 24, 1967 (see the **Federal Register** of October 31, 1967 (32 FR 15046)).

Bromfenac sodium: All drug products containing bromfenac sodium. The use of bromfenac sodium, formerly marketed as Duract capsules, was associated with fatal hepatic failure. Duract capsules were voluntarily withdrawn from the market by their manufacturer on June 22, 1998.

Butamben: All parenteral drug products containing butamben. The use of a parenteral drug product containing butamben, formerly marketed as Efocaine, was associated with severe adverse reactions, such as severe tissue slough and transverse myelitis.

Approval of the NDA for Efocaine was withdrawn on August 7, 1964 (see the **Federal Register** of August 14, 1964 (29 FR 11656)).

Camphorated oil: All drug products containing camphorated oil. Products containing camphorated oil were associated with poisoning in infants and young children due to accidental ingestion. FDA directed the removal from the market of drug products containing camphorated oil in 1982 (see 21 CFR 310.526 (1997)).

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate. Carbetapentane citrate gel, formerly marketed as Candette Cough Jel, was determined not to be safe because the inexact methods of measuring the gel by consumers were potentially dangerous. Approval of the NDA for Candette Cough Jel was withdrawn on November 29, 1972 (see the **Federal Register** of November 29, 1972 (37 FR 25249)).

Casein, iodinated: All drug products containing iodinated casein. Iodinated casein, formerly marketed as a component of Neo-Barine, was associated with thyrotoxic side effects. Approval of the NDA for Neo-Barine was withdrawn October 22, 1964 (see the **Federal Register** of October 28, 1964 (29 FR 14676)).

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation. Chlorhexidine gluconate topical tincture 0.5%, formerly marketed as Hibitane, was associated with chemical and thermal burns when used as a patient preoperative skin preparation. The drug product was voluntarily removed from the market in early 1984. FDA determined that chlorhexidine gluconate topical tincture 0.5% was removed from the market for reasons of safety (see the **Federal Register** of October 6, 1997 (62 FR 52137)).

Chlormadinone acetate: All drug products containing chlormadinone acetate. Chlormadinone acetate, formerly marketed as a component of the combination drug products Estalor-21 and C-Quens tablets, was associated with the development of mammary tumors in dogs. The manufacturer ceased marketing the drug in 1970 and approvals of the NDA's for Estalor-21 and C-Quens tablets were withdrawn by FDA on March 16, 1972 (see the **Federal Register** of March 16, 1972 (37 FR 5516)).

Chloroform: All drug products containing chloroform. National Cancer Institute studies demonstrated that chloroform is carcinogenic in animals. FDA directed the removal from the market of drug products containing chloroform in 1976 (see 21 CFR 310.513 (1997)).

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives). FDA found that cobalt salts were not safe or effective for treatment of iron-deficiency anemia. The toxic effects of cobalt salts include liver damage, claudication, and myocardial damage. FDA directed the removal from the market of drug products containing cobalt salts in 1967 (see 21 CFR 250.106 (1997)).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride. Dexfenfluramine hydrochloride, formerly marketed as Redux capsules, was associated with valvular heart disease. The manufacturer of dexfenfluramine hydrochloride capsules voluntarily withdrew the drug from the market in September 1997.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride. Diamthazole dihydrochloride, formerly marketed as Asterol ointment, powder, and tincture, was associated with neurotoxicity. Approvals of the NDA's for Asterol ointment, powder, and tincture were withdrawn on July 19, 1977 (see the **Federal Register** of July 19, 1977 (42 FR 37057)).

Dibromsalan: All drug products containing dibromsalan. Dibromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing dibromsalan in 1975 (see § 310.508 (21 CFR 310.508) (1997)).

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams (mg) or more of diethylstilbestrol per unit dose. Diethylstilbestrol, marketed in various tablet and parenteral drug products, was associated with adenocarcinoma of the vagina in the offspring of the patient when used in early pregnancy. Approvals of the NDA's for these diethylstilbestrol drug products were withdrawn on February 18, 1975 (see the **Federal Register** of February 5, 1975 (40 FR 5384)).

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate. Dihydrostreptomycin sulfate, formerly marketed in several parenteral drug products, was associated with ototoxicity. Approvals of the NDA's for dihydrostreptomycin sulfate drug products were withdrawn on July 20, 1970 (see the **Federal Register** of September 3, 1970 (35 FR 13988)).

Dipyrone: All drug products containing dipyrone. Dipyrone, formerly marketed as Dimethone tablets and injection, Protemp oral liquid, and other drug products, was associated with potentially fatal agranulocytosis. Approvals of the NDA's for dipyrone drug products were withdrawn on June 27, 1977 (see the **Federal Register** of June 17, 1977 (42 FR 30893)).

Encainide hydrochloride: All drug products containing encainide hydrochloride. Encainide hydrochloride, formerly marketed as Enkaid capsules, was associated with increased death rates in patients who had asymptomatic heart rhythm abnormalities after a recent heart attack. The manufacturer of Enkaid capsules voluntarily withdrew the product from the market on December 16, 1991.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride. Fenfluramine hydrochloride tablets, formerly marketed as Pondimin tablets, were associated with valvular heart disease. The manufacturer of fenfluramine hydrochloride tablets voluntarily withdrew the drug from the market in September 1997.

Flosequinan: All drug products containing flosequinan. Flosequinan, formerly marketed as Manoplax tablets, was the subject of a study that indicated the drug had adverse effects on survival, and that beneficial effects on the symptoms of heart failure did not last beyond the first 3 months of therapy. After the first 3 months of therapy, patients on the drug had a higher rate of hospitalization than patients taking a placebo. The manufacturer of Manoplax tablets voluntarily withdrew the drug from the market in July 1993.

Gelatin: All intravenous drug products containing gelatin. Gelatin for intravenous use, formerly marketed as Knox Special Gelatine Solution Intravenous-6 percent, was found not to be suitable as a plasma expander because the drug caused increased blood viscosity, reduced blood clotting, and prolonged bleeding time. Approval of the NDA for Knox Special Gelatine Solution Intravenous-6 percent was withdrawn on April 19, 1978 (see the **Federal Register** of April 7, 1978 (43 FR 14743)).

Glycerol, iodinated: All drug products containing iodinated glycerol. Iodinated glycerol, formerly marketed as Iodur Elixir and other drug products, was

found to have carcinogenic potential. FDA directed the removal from the market of drug products containing iodinated glycerol in April 1993.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin. Chorionic gonadotropins of animal origins, formerly marketed as Synapoidin Steri-Vial, were shown to produce allergic reactions. Approval of the NDA for Synapoidin Steri-Vial was withdrawn on July 6, 1972 (see the **Federal Register** of July 6, 1972 (37 FR 13284)).

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate. Mepazine hydrochloride, formerly marketed as Pacatal tablets, and mepazine acetate, formerly marketed as Pacatal for injection, were associated with granulocytopenia, granulocytosis, paralytic ileus, urinary retention, seizures, hypotension, and jaundice. Approval of the NDA for Pacatal tablets and Pacatal for injection was withdrawn on May 28, 1970 (see the **Federal Register** of May 28, 1970 (35 FR 8405)).

Metabromsalan: All drug products containing metabromsalan. Metabromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing metabromsalan in 1975 (see § 310.508 (1997)).

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride. Parenteral methamphetamine hydrochloride, formerly marketed as Methedrine injection and Drinalfa injection and used as an adjunct treatment for weight reduction, was found to have a history of serious abuse and a severe risk of dependence. Approvals of the NDA's for Methedrine injection and Drinalfa injection were withdrawn on March 30, 1973 (see 21 CFR 310.504 (1997)).

Methapyrilene: All drug products containing methapyrilene. Methapyrilene, formerly marketed in many drug products, was shown to be a potent carcinogen. Manufacturers voluntarily withdrew methapyriline drug products from the market in May and June 1979.

Methopholine: All drug products containing methopholine. Methopholine, formerly marketed as Versidyne tablets, was associated with ophthalmic changes and corneal opacities in dogs. Approval of the NDA for Versidyne tablets was withdrawn on March 22, 1965 (see the **Federal Register** of March 27, 1965 (30 FR 4083)).

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride. Mibefradil dihydrochloride, formerly marketed as Posicor tablets, was associated with potentially harmful interactions with other drugs. Mibefradil dihydrochloride reduced the activity of certain liver enzymes that are important in helping the body eliminate many other drugs. Inhibiting these enzymes can cause some of these drugs to accumulate to dangerous levels in the body. The manufacturer voluntarily removed Posicor tablets from the market on June 8, 1998.

Neomycin sulfate: All parenteral drug products containing neomycin sulfate. Parenteral neomycin sulfate was found to present toxicity problems when used to irrigate wounds and was found not to be acceptable for the treatment of urinary tract infections due to the availability of newer, safer antibiotics that were as effective as, or more effective than, parenteral neomycin sulfate. Approvals of the marketing applications for parenteral neomycin sulfate were withdrawn on January 5, 1989 (see the **Federal Register** of December 6, 1988 (53 FR 49232)).

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application). Nitrofurazone, formerly marketed in nasal drops, otic drops, and vaginal suppositories, was associated with mammary neoplasia in rats. Approvals of the NDA's for the nitrofurazone drug products were withdrawn on December 4, 1974, and June 10, 1975 (see the **Federal Register** of December 4, 1974 (39 FR 42018), and May 30, 1975 (40 FR 23502)).

Nomifensine maleate: All drug products containing nomifensine maleate. Nomifensine maleate, formerly marketed as Merital capsules, was associated with an increased incidence of hemolytic anemia. The approved application holder removed Merital capsules from the market on January 23, 1986. FDA published a notice of its determination that Merital capsules were removed from the market for safety reasons (see the **Federal Register** of June 17, 1986 (51 FR 21981)). Approval of the NDA for Merital capsules was withdrawn on March 20, 1992 (see the **Federal Register** of March 20, 1992 (57 FR 9729)).

Oxyphenisatin: All drug products containing oxyphenisatin. Oxyphenisatin, formerly marketed in Lavema Compound Solution and Lavema Enema Powder, was associated with hepatitis and jaundice. The approvals of the NDA's for Lavema Compound Solution and Lavema Enema Powder were withdrawn on March 9, 1973 (see the **Federal Register** of March 9, 1973 (38 FR 6419)).

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate. Oxyphenisatin acetate, formerly marketed in Dialose Plus capsules, Noloc capsules, and other drug products, was associated with hepatitis and jaundice. Approvals of the NDA's for the oxyphenisatin acetate drug products were withdrawn on February 1, 1972 (see the **Federal Register** of February 1, 1972 (37 FR 2460)).

Phenacetin: All drug products containing phenacetin. Phenacetin, formerly marketed in A.P.C. with Butalbital tablets and capsules and other drug products, was associated with a high potential for harm to the kidneys and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse. The approvals of the NDA's for the phenacetin drug products were withdrawn on November 4, 1983 (see the **Federal Register** of October 5, 1983 (48 FR 45466)).

Phenformin hydrochloride: All drug products containing phenformin hydrochloride. Phenformin hydrochloride, formerly marketed as D.B.I. tablets, Meltrol-50 capsules, and other drug products, was associated with lactic acidosis. Approvals of the NDA's for the phenformin hydrochloride drug products were withdrawn on November 15, 1978 (see the **Federal Register** of April 6, 1979 (44 FR 20967)).

Pipamazine: All drug products containing pipamazine. Pipamazine, formerly marketed as Mornidine tablets and injection, was associated with hepatic lesions. Approval of the NDA for Mornidine tablets and injection was withdrawn on July 17, 1969 (see the **Federal Register** of July 17, 1969 (34 FR 12051)).

Potassium arsenite: All drug products containing potassium arsenite. Potassium arsenite, formerly marketed as Fowler's Solution (oral), was toxic and highly carcinogenic. FDA determined Fowler's Solution was a new drug in April 1980, and the manufacturers removed the drug product from the market.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 mg or more of potassium per dosage unit

(except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion). Concentrated solid oral dosage forms of potassium salt were associated with small bowel lesions. Approvals of NDA's for all solid oral dosage form drug products containing potassium chloride that supply 100 mg or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion) were withdrawn on July 29, 1977, and April 29, 1992 (see the **Federal Register** of July 29, 1977 (42 FR 38644), and April 29, 1992 (57 FR 18157)).

Povidone: All intravenous drug products containing povidone. Povidone, marketed as Polyvinylpyrrolidone in Normal Saline, was found to be unsafe for use as a plasma expander in the emergency treatment of shock because povidone accumulates in the body and may cause storage disease with the formation of granulomas. Povidone also interferes with blood coagulation, hemostasis, and blood typing and cross matching. Approval of the NDA for Polyvinylpyrrolidone in Normal Saline was withdrawn on April 19, 1978 (see the **Federal Register** of April 7, 1978 (43 FR 14743)).

Reserpine: All oral dosage form drug products containing more than 1 mg of reserpine. Reserpine, marketed as Reserpoid tablets, Rau-Sed tablets, and other drug products for the treatment of hypertension and psychiatric disorders, was associated with a greater frequency and severity of adverse effects in strengths greater than 1 mg. Approvals of NDA's, or those portions of NDA's, for solid oral dosage form drug products containing more than 1 mg of reserpine were withdrawn on May 9, 1977 (see the **Federal Register** of April 29, 1977 (42 FR 21844)).

Sparteine sulfate: All drug products containing sparteine sulfate. Sparteine sulfate, formerly marketed as Spartocin injection and Tocosamine sterile solution, was found to have unpredicatable effects and was associated with tetanic uterine contractions and obstetrical complications. Approvals of the NDA's for Spartocin injection and Tocosamine sterile solution were withdrawn on August 17, 1979 (see the **Federal Register** of August 7, 1979 (44 FR 46316)).

Sulfadimethoxine: All drug products containing sulfadimethoxine. Sulfadimethoxine, formerly marketed in Madricidin capsules, was associated with Stevens-Johnson syndrome and fatalities. Approval of the NDA for Madricidin capsules was withdrawn on March 11, 1966 (see the **Federal Register** of March 19, 1966 (31 FR 4747)).

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use). Sulfathiazole, formerly marketed in Tresamide tablets and several other brands of tablets, was associated with renal complications, rash, fever, blood dyscrasias, and liver damage. Approvals of the NDA's for sulfathiazole tablets were withdrawn on September 28, 1970 (see the **Federal Register** of October 15, 1970 (35 FR 16190)).

Suprofen: All drug products containing suprofen (except ophthalmic solutions). Suprofen, formerly marketed as Suprol capsules, was associated with flank pain syndrome. The manufacturer voluntarily removed Suprol capsules from the market in May 1987.

Sweet spirits of nitre: All drug products containing sweet spirits of nitre. Sweet spirits of nitre, also known as spirit of nitre, spirit of nitrous ether, and ethyl nitrite spirit, was associated with methemoglobinemia in infants. FDA directed the removal from the market of drug products containing sweet spirits of nitre in 1980 (see 21 CFR 310.525 (1997)).

Temafloxacin hydrochloride: All drug products containing temafloxacin hydrochloride. Temafloxacin hydrochloride, formerly marketed as Omniflox tablets, was associated with hypoglycemia in elderly patients, as well as a constellation of multisystem organ involvement characterized by hemolytic anemia, frequently associated with renal failure, markedly abnormal liver tests, and coagulopathy. The approved application holder voluntarily removed Omniflox tablets from the market in Spring 1992. Approval of the NDA for Omniflox tablets was withdrawn on September 25, 1997 (see the **Federal Register** of September 25, 1997 (62 FR 50387)).

Terfenadine: All drug products containing terfenadine. Terfenadine, formerly marketed in Seldane and Seldane-D tablets, was associated with serious heart problems when used concurrently with certain drugs, including certain antibiotics and antifungals. Seldane and Seldane-D tablets were voluntarily removed from the market by their manufacturer in February 1998.

3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalicylanilide. The halogenated salicylanilide 3,3′,4′,5-tetrachlorosalicylanilide, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing 3,3′,4′,5-tetrachlorosalicylanilide in 1975 (see § 310.508 (1997)).

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 mg/milliliter (mL). Concentrated tetracycline was associated with temporary inhibition of bone growth, permanent staining of the teeth, and enamel hypoplasia in children. FDA amended the antibiotic drug regulations so that drug products containing tetracycline formulated for pediatric use in a concentration greater than 25 mg/mL would not be certified (see the **Federal Register** of October 31, 1978 (43 FR 50676)).

Ticrynafen: All drug products containing ticrynafen. Ticrynafen, formerly marketed as Selacryn tablets, was associated with liver toxicity. Selacryn tablets were voluntarily withdrawn from the market by their manufacturer on January 16, 1980. Approval of the NDA for Selacryn tablets was withdrawn on May 20, 1996 (see the **Federal Register** of May 20, 1996 (61 FR 25228)).

Tribromsalan: All drug products containing tribromsalan. Tribromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing tribromsalan in 1975 (see § 310.508 (1997)).

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane. Trichloroethane is potentially toxic to the cardiovascular system and was associated with deaths from misuse or abuse. FDA directed the removal from the market of aerosal drug products intended for inhalation containing trichloroethane in 1977 (see 21 CFR 310.507 (1997)).

Urethane: All drug products containing urethane. Urethane (also known as urethan and ethyl carbamate), formerly marketed as an inactive ingredient in Profenil injection, was determined to be carcinogenic. Approval of the NDA for Profenil

injection was withdrawn on March 28, 1977 (see the **Federal Register** of March 18, 1977 (42 FR 15138)).

Vinyl chloride: All aerosol drug products containing vinyl chloride. The inhalation of vinyl chloride is associated with acute toxicity manifested by dizziness, headache, disorientation, and unconsciousness. FDA directed the removal from the market of aerosol drug products containing vinyl chloride in 1974 (see 21 CFR 310.506 (1997)).

Zirconium: All aerosol drug products containing zirconium. Zirconium, formerly used in several aerosol drug products as an antiperspirant, was associated with human skin granulomas and toxic effects in the lungs and other internal organs of test animals. FDA directed the removal from the market of aerosol drug products containing zirconium in 1977 (see 21 CFR 310.510 (1997)).

Zomepirac sodium: All drug products containing zomepirac sodium. Zomepirac sodium, formerly marketed as Zomax tablets, was associated with fatal and near-fatal anaphylactoid reactions. The manufacturer voluntarily removed Zomax tablets from the market in March 1983.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the following paragraphs, the agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this proposal because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. Although the agency is not aware of any routine use of these drug products in pharmacy compounding, the agency invites the submission of comments on this issue and solicits current compounding usage data for these drug products.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with Section 503A of the act. This provision specifically directs FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this proposal will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any further loss of sales due to this proposal. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than $5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal Governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of $100 million annually. Because the agency does not estimate any annual expenditures due to the proposed rule, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (Pub. L. 104–13) is not required.

VII. Request for Comments

Interested persons may, on or before November 23, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The agency notes that the comment period in this document is shorter than the 75-day period that is customarily provided by FDA for proposed rules of a technical nature. Likewise, this comment period is less than the 60 days ordinarily provided, as set out in FDA's procedural regulations, § 10.40(b)(2) (21 CFR 10.40(b)(2)). As discussed in the following paragraphs, FDA believes that a 45-day comment period is appropriate in this instance. Executive Order 12889 (58 FR 69681, December 30, 1993), which implemented the North American Free Trade Agreement, states that any agency subject to the Administrative Procedure Act should provide a 75-day comment period for any proposed Federal technical regulation or any Federal sanitary or phytosanitary measure of general application. However, Executive Order 12889 provides an exception to the 75-

day period where the United States considers the measure necessary to address an urgent problem related to the protection of human, plant, or animal health. Similarly, FDA regulations establish a 60-day comment period as ordinary agency practice, but provide that the 60-day period may be shortened if the Commissioner of Food and Drugs finds good cause for doing so.

As discussed in this document, section 503A(a) of the act exempts certain compounded drug products from some specific misbranding and adulteration provisions, as well as the new drug provision, of the act. Section 503A(b)(1)(C) of the act excludes from the exemption drugs that FDA has found were removed from the market or had marketing applications withdrawn because the drug product or some component of the drug product was unsafe or ineffective. Compounding versions of many of these drug products presents a serious risk to human health, either indirectly, because a patient is being provided an ineffective drug product when effective drug products may be available, or directly, due to the toxicity of the drug product. Indeed, many of the drug products listed in this proposed rule have been associated with human fatalities.

Section 127(b) of the Modernization Act provides that section 503A of the act will go into effect on November 21, 1998. If a final regulation issuing the list of drug products that have been withdrawn or removed is not published before November 21, 1998, these drug products may be compounded, exempt from various legal requirements, contrary to the expressed intent of Congress and at a risk to human health. Accordingly, the agency intends to solicit public comment on this proposal, consider the comments submitted, and prepare and publish a final implementing regulation by November 21, 1998. FDA has concluded that the urgency of this matter is sufficient justification for shortening the comment period for this proposal to 45 days, consistent with Executive Order 12889. Similarly, this urgency constitutes good cause within the meaning of § 10.40(b), which justifies shortening the period to 45 days.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be added to read as follows:

1. Part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyrone: All drug products containing dipyrone.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Neomycin sulfate: All parenteral drug products containing neomycin sulfate.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Pipamazine: All drug products containing pipamazine.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Temafloxacin hydrochloride: All drug products containing temafloxacin hydrochloride.

Terfenadine: All drug products containing terfenadine.

3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Urethane: All drug products containing urethane.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: October 1, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–26923 Filed 10–2–98; 4:25 pm]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[PA–4076b; FRL–6166–2]

Approval and Promulgation of Air Quality Implementation Plans; Pennsylvania; Approval of VOC and NO_X RACT Determinations for Individual Sources

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to approve the State Implementation Plan (SIP) revision submitted by the Commonwealth of Pennsylvania for the purpose of establishing volatile organic compound (VOC) and nitrogen oxides (NO_X) reasonably available control technology (RACT) for four (4) major sources located in Pennsylvania. In the Final Rules section of this **Federal Register**, EPA is approving the Commonwealth's SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial SIP revision and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule and the accompanying technical support document. If no adverse comments are received in response to this rule, no further activity is contemplated in relation to this rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this action. Any parties interested in commenting on this action should do so at this time. If adverse comments are received that do not pertain to all documents subject to this rulemaking action, those documents not affected by the adverse comments will be finalized in the manner described here. Only those documents that receive adverse comments will be withdrawn in the manner described here.

DATES: Comments must be received in writing by November 9, 1998.

ADDRESSES: Written comments should be addressed to David Campbell, Air Protection Division, Mailcode 3AP11, U.S. Environmental Protection Agency, Region III, 1650 Arch St., Philadelphia, Pennsylvania 19103. Copies of the documents relevant to this action are available for public inspection during normal business hours at the Air Protection Division, U.S. Environmental Protection Agency, Region III, 1650 Arch St., Philadelphia, Pennsylvania 19103; and the Pennsylvania Department of Environmental Protection, Bureau of Air Quality Control, P.O. Box 8468, 400 Market Street, Harrisburg, Pennsylvania 17105.

FOR FURTHER INFORMATION CONTACT: David Campbell, (215) 814–2196, at the EPA Region III office or via e-mail at campbell.dave@epamail.epa.gov. While information may be requested via e-mail, comments must be submitted in writing to the above Region III address.

SUPPLEMENTARY INFORMATION: See the information pertaining to this action, VOC and NO_X RACT determinations for individual sources located in Pennsylvania, provided in the Direct Final action of the same title which is located in the Rules and Regulations Section of this **Federal Register**.

Authority: 42 U.S.C. 7401–7671q.

Dated: September 11, 1998.

W. Michael McCabe,

Regional Administrator, Region III.

[FR Doc. 98–26896 Filed 10–7–98; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[TN–201–9828b; FRL–6169–7]

Approval and Promulgation of Implementation Plans Tennessee: Approval of Revisions to the Nashville/Davidson County Portion of the Tennessee SIP Regarding Control of Volatile Organic Compounds

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The EPA proposes to approve revisions to the Nashville/Davidson County portion of the Tennessee State Implementation Plan (SIP) concerning control of volatile organic compounds. The State of Tennessee through the Tennessee Department of Air Pollution Control submitted the revisions to EPA on July 23, 1997. To be consistent with the EPA's Guidelines for ''Control of Volatile Organic Compounds Emissions from Stationary Sources,'' the State of Tennessee amended Regulation No. 7, ''Regulation for Control of Volatile Organic Compounds, Section 7–16, Emission Standards for Surface Coating of Miscellaneous Metal Parts and Products'' of the Nashville/Davidson County portion of the Tennessee SIP (Nashville SIP).

In the final rules section of this **Federal Register**, the EPA is approving the State of Tennessee SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial revision amendment and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule. If no adverse comments are received in response to the direct final rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. The EPA will not institute a second comment period on this document. Any parties interested in commenting on this document should do so at this time.

DATES: To be considered, comments must be received by November 9, 1998.

ADDRESSES: Written comments should be addressed to Mr. Gregory O. Crawford at the EPA Regional Office listed below. Copies of documents relative to this action are available for public inspection during normal business hours at the following locations. The interested persons

APPENDIX 14:

Olefin polymers	Density	Melting Point (MP) or softening point (SP) (*Degrees Centigrade*)	Maximum extractable fraction (expressed as percent by weight of the polymer) in *N*-hexane at specified temperatures	Maximum soluble fraction (expressed as percent by weight of polymer) in xylene at specified temperatures
*	*	*	*	*
3.7 Ethylene/propylene copolymers, meeting the identity described in paragraph (a)(3)(i) of this section, containing not less than 80 mole-percent of polymer units derived from ethylene and having a minimum viscosity average molecular weight of 95,000 as determined by the method described in paragraph (d)(5) of this section, and a minimum Mooney viscosity of 13 as determined by the method described in paragraph (d)(6) of this section. Ethylene/propylene copolymers described in this item 3.7 are to be used only in blends with other olefin polymers complying with this section, at levels not to exceed 30 percent by weight of the total polymer blend, and in contact with food only of types identified in § 176.170(c) of this chapter, Table 1, under Types I, II, III, IV–B, VI, VII, VIII, and IX. Additionally, optional adjuvants permitted for use in olefin copolymers complying with item 3.4 of this table may be used in the production of this copolymer.	Not less than 0.86			
*	*	*	*	*

* * * * *

Dated: February 23, 1999.

Janice F. Oliver,

Deputy Director for Systems and Support, Center for Food Safety and Applied Nutrition.

[FR Doc. 99–5520 Filed 3–5–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N–0655]

List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to include a list of drug products that may not be used for pharmacy compounding under the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

DATES: This rule is effective on April 7, 1999.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers

Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

Section 127 of the Modernization Act (Pub. L. 105–115), which added section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. Section 503A(b)(1)(C) of the act provides that the licensed pharmacist or licensed physician does not ''compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.'' Section 503A(d)(1) of the act requires that the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective be issued as a regulation and that an advisory committee be consulted in the rulemaking process.

In the **Federal Register** of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective. The primary focus of that initial proposed rule and this final rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may initiate rulemaking to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective or to update the list as new information becomes available to the agency regarding products that were removed from the market because they were unsafe. The proposed rule was presented to the Pharmacy Compounding Advisory Committee at a meeting held on October 14 and 15, 1998 (see the **Federal Register** of September 4, 1998 (63 FR 47301)). The committee did not have any adverse comments on the proposed rule and did not suggest any changes.

II. Comments on the Proposed Rule

FDA received comments from consumers, pharmacists, a medical doctor, a pharmaceutical manufacturer, a pharmaceutical manufacturers' organization, and a committee representing the plaintiffs in a drug product liability class action suit.

1. Two comments questioned FDA's shortening the comment period from 75 to 45 days.

As FDA stated in the preamble to the proposed rule (63 FR 54082 at 54087 to 54088), the agency believes that a shorter comment period was warranted to expedite this rulemaking proceeding because the compounding of many of the drug products on the list would present a serious threat to the public health. Many of the drug products have caused death or life-threatening conditions. Some of the drugs on the list are believed to cause cancer, while others were shown to be toxic to the liver and other organs.

2. One comment objected to the wording of the first sentence of proposed § 216.24, which says ''The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective.'' The comment expressed concerns that the finding that a drug was withdrawn from the market by the manufacturer because it was not safe or effective might be used in a product liability lawsuit against the manufacturer who voluntarily withdrew the drug product from the market. The comment also expressed concerns that fear of having the finding used against them might discourage manufacturers from voluntarily withdrawing drug products when concerns about the drug product's safety and effectiveness have developed.

The agency does not believe it is necessary to change the wording of § 216.24 in response to this comment. Compounding pharmacists and physicians are the intended audience for this rule. The purpose of § 216.24 is to provide these compounders a list of drugs that they may not compound under section 503A of the act. This list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.

For the purposes of this rule, FDA has determined that it is not necessary to deviate from the statutory language found in section 503A(b)(1)(C) of the act, which prohibits compounders from compounding ''a drug product that appears on a list published by [FDA] in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or ineffective.''

The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

3. A large number of comments objected to drug products containing adrenal cortex being placed on the list. One of the comments included a photocopy of an article from the November issue of the magazine *Nutrition & Healing*. This article apparently is the source of much of the content of many of the comments. None of the comments provided any information about the removal of adrenal cortex extract from the market, other than the unsupported statements that the removal of adrenal cortex extract was economically motivated. These comments included unsupported statements that adrenal cortex extract has never been associated with a death or serious adverse event (except for a series of adverse events in 1996 and 1997 associated with contaminated adrenal cortex extract) and that adrenal cortex extract is safer and more effective than the synthetic adrenocortical steroids that have replaced it in medical use. The comments also asserted, without presenting any scientific data or historical information to support the assertion, that FDA acted improperly in directing the removal of drugs containing adrenal cortex from the market because the low levels of corticosteroids found in the drugs presented a substantial risk of undertreatment of serious conditions.

FDA's concerns about the safety of adrenal cortex extract have grown stronger since the drug product was removed from the market in 1978. Adrenal cortex extract is derived from the cortex adrenal glands of domestic food animals, including cattle. In 1986 the disease bovine spongiform encephalopathy (BSE) was identified in cattle. BSE has been found to be epidemic in Great Britain and present in Western Europe and Oman. Hundreds of thousands of cattle have either died or been destroyed as a result of BSE infection. Since that time strong evidence has been developed associating ingestion of tissues from

BSE-infected cattle with the development of new variant Creutzfeldt–Jakob disease (nvCJD) in humans. A patient taking a drug derived from the adrenal cortex of a BSE-infected cow would be running an unacceptable risk of contracting nvCJD. Due to the destruction of BSE-infected cattle and other controls (see the **Federal Register** of August 29, 1994 (59 FR 44591)), the chances of a patient getting nvCJD from adrenal cortex extract are low. However, there is still a risk involved in taking adrenal cortex extract, and that risk must be taken very seriously in light of the fact that nvCJD appears to always be fatal.

Concerning the comments that FDA acted improperly in removing drugs containing adrenal cortex from the market because of a substantial risk of undertreatment of serious conditions, FDA's action was investigated by the General Accounting Office and found to be proper (see ''By the Comptroller General, Report to the Honorable Barry M. Goldwater, Jr., House of Representatives of the United States: Adrenal Cortical Extract Taken Off Drug Market'' (HRD–81–61, 1981)).

For the reasons stated previously, FDA is keeping drug products containing adrenal cortex on the list of drugs that may not be compounded under section 503A of the act.

4. One comment strongly supported the inclusion of drug products containing dexfenfluramine hydrochloride and fenfluramine hydrochloride on the list.

5. One comment pointed out that there is a hearing request pending before the agency regarding the withdrawal of approval of the applications for neomycin sulfate in sterile vials for injection (see the **Federal Register** of December 6, 1988 (53 FR 49232)) and another pending request for a hearing regarding the withdrawal of approval of the applications for neomycin sulfate for prescription compounding (see the **Federal Register** of December 6, 1988 (53 FR 49231)). A petition for stay of action regarding the two actions mentioned above and regarding a labeling guideline for neomycin sulfate for prescription compounding (see the **Federal Register** of April 15, 1988 (53 FR 12662)) is also pending before the agency.

Because of the complex administrative record on neomycin sulfate currently before the agency and because of the public health need to expedite implementation of this rule, FDA is postponing final action on listing all parenteral drug products containing neomycin sulfate. Parenteral drug products containing neomycin sulfate may be added to the list at a later date.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the paragraphs below, the agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this final rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. The agency is not aware of any routine use of these drug products in pharmacy compounding and received no significant data in response to the request in the preamble to the proposed rule for the submission of comments on this issue and current compounding usage data for these drug products. Additionally, FDA did not receive any comments on compliance costs and loss of sales due to this rule or current compounding usage data for the drug products listed in this rule at the Pharmacy Compounding Advisory Committee meeting held on October 14 and 15, 1998.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with section 503A of the act. This provision specifically directs the FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this final rule will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any loss of sales due to this rule. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than $5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before it finalizes any rule requiring any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of $100 million annually. Because the agency does not estimate any annual expenditures due to the final rule, FDA is not required to

perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyrone: All drug products containing dipyrone.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Pipamazine: All drug products containing pipamazine.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Temafloxacin hydrochloride: All drug products containing temafloxacin.

Terfenadine: All drug products containing terfenadine.

3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Urethane: All drug products containing urethane.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: March 1, 1999.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 99–5517 Filed 3–5–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 874

[Docket No. 98N–0249]

Ear, Nose, and Throat Devices; Classification of the Nasal Dilator, the Intranasal Splint, and the Bone Particle Collector

AGENCY: Food and Drug Administration, HHS.

APPENDIX 15:

MEMORANDUM

TO: **Division of Dockets Management, HFA-305**

FROM: **Nancy K. Hayes**
Office of Regulatory Policy (ORP)
Center for Drug Evaluation and Research (CDER)

RE: **Docket Nos.** FDA-1979-N-0256/PSA1, FDA-1979-N-0256/PSA2, FDA-1979-N-0220/PSA1, FDA-1987-D-0240/PSA1

DATE: **August 6, 2012**

Please consider the citizen petitions in the above-referenced dockets to have been voluntarily withdrawn without prejudice to resubmission. The petitions for stay of action, dated August 12, 1988 (three petitions) and December 30, 1988, were submitted by Pharma-Tek, Inc., which is now known as X-Gen Pharmaceuticals, Inc.

On June 18, 2012, CDER-ORP sent a letter to the petitioner via certified mail (return-receipt requested) requesting that the petitioner affirmatively inform CDER if the petitioner wanted the petitions to remain active. The letter stated that if we do not receive a written response within 30 days from the date of the letter, a copy of the letter would be filed in the respective dockets with instructions that the petitions be considered to have been voluntarily withdrawn without prejudice to resubmission.

The signed return receipt from the certified mailing was received by CDER-ORP on June 25, 2012. To date, the petitioner has not responded to the Agency. In light of the above, we are considering the petitions to be voluntarily withdrawn without prejudice, and we request closure of these dockets.

The letter and signed return receipt are attached to this memorandum.

Attachments: June 18, 2012, Letter from Nancy K. Hayes (ORP) to Susan Badia
certified, return-receipt requested

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

JUN 18 2012

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Susan Badia
President and CEO
X-Gen Pharmaceuticals, Inc.
Post Office Box 445
Big Flats, New York 14814

Re: Docket Nos. FDA-1979-N-0256/PSA1, FDA-1979-N-0256/PSA2, FDA-1979-N-0220/PSA1, FDA-1987-D-0240/PSA1 (neomycin sulfate)[1]

Dear Ms. Badia:

According to our records, the petitions referenced above, requesting a stay of action regarding withdrawal of approval of the applications for neomycin sulfate products, have not been resolved.[2] We have enclosed copies of the petitions for ease of reference.

As part of the Agency's efforts to reduce the backlog of unresolved citizen petitions, the Center for Drug Evaluation and Research (CDER or the Center) periodically reviews unresolved petitions assigned to it for action. One goal of these reviews is to identify citizen petitions submitted more than 5 years ago that, as a result of subsequent events, no longer appear to raise significant and current public health issues. CDER believes that having to respond to outdated petitions that do not have current public health implications diminishes the Center's capacity to address in a timely fashion petitions that raise important and current public health issues, as well as its capacity to perform its many other duties. Therefore, older petitions that no longer have public health implications have a low priority, and it is unlikely that the Center will have the resources to respond to them soon.

The petitions referenced above were submitted more than 20 years ago, and a review of the dockets shows that they have been inactive for many years. The petitions request that the Agency refrain from withdrawing approval of the applications for neomycin sulfate products; the approvals of these applications have not been withdrawn and these products remain on the market. Therefore, CDER does not believe that these petitions raise significant and current public health issues that merit a formal Agency response.

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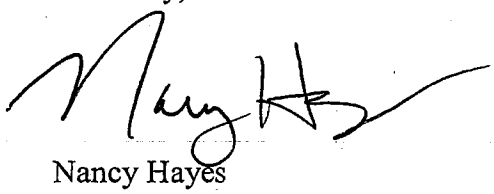
[1] These citizen petitions were originally assigned docket numbers 1979N-0151/PSA1, 1979N-0151/PSA2, 1979N-0155/PSA1, 1987D-0315/PSA1, respectively. The numbers were changed to FDA-1979-N-0256/PSA1, FDA-1979-N-0256/PSA2, FDA-1979-N-0220/PSA1, FDA-1987-D-0240/PSA1, respectively, as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] 1979N-0151/PSA1, 1979N-0151/PSA2, 1979N-0155/PSA1, 1987D-0315/PSA1 were submitted to FDA by Pharma-Tek, Inc., which subsequently became X-Gen Pharmaceuticals, Inc.

Accordingly, we would appreciate if you would review the petitions and respond to the docket numbers listed above if you wish to keep these petitions active. If we do not receive a written response from you within 30 days from the date of this letter, a copy of this letter will be filed in the respective dockets, with instructions that the petitions be considered to have been voluntarily withdrawn without prejudice to resubmission.

If you have any questions, please contact me at 301-796-3602. Thank you for your attention to this matter.

Sincerely,



Nancy Hayes
Director, Division of Regulatory Policy I
Office of Regulatory Policy
Center for Drug Evaluation and Research

Enclosures

APPENDIX 16:

ORIG-1
SD # 43

ANDA 61579

09 October 2015

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

Re: Withdrawal of Dockets FDA-1979-N-0256, FDA-1979-N-0220, and FDA-1987-D-0240 Neomycin Sulfate Powder for Prescription Compounding; Pharma-Tek, Inc. Request for Hearing

Dear FDA Authorized Representative,

X-GEN Pharmaceuticals, Inc. is hereby submitting a withdrawal of our hearing requests filed on behalf of Pharma-Tek, Inc. concerning the Dockets FDA-1979-N-0256, FDA-1979-N-0220, and FDA-1987-D-0240[2].

X-GEN Pharmaceuticals, Inc. agrees to withdraw our existing hearing requests, and waive the opportunity for a hearing and permit FDA to withdraw approval of our application under 21 CFR 314.150(d) for the compound nonsterile neomycin sulfate drug product under ANDA 61-579.

X-Gen Pharmaceuticals, Inc. certifies that this submission is virus free as tested by AVG (Version 10.0.1209, Virus Database: 1500/3554).

As of May 2009, X-Gen Pharmaceuticals, Inc. has an updated letter of non-repudiation on file with the FDA.

If you have any questions regarding the information included within this submission please direct correspondence to me per the contact information shown in the signature line.

Yours truly,

Heather M. Mahosky

Heather Mahosky
Regulatory Affairs Specialist
X-GEN Pharmaceuticals, Inc.
Ph: (607) 562-2700 | Fx: (607)562-2760
hmahosky@x-gen.us | regulatory@x-gen.us |www.x-gen.us

45678

APPENDIX 17:

Application No.	Drug	Applicant
ANDA 077895	Ursodiol Capsules USP, 300 mg	Impax Laboratories, LLC, 30831 Huntwood Ave., Hayward, CA 94544.
ANDA 078810	Oxaliplatin for Injection, 50 mg/vial and 100 mg/vial	Fresenius Kabi Oncology Plc., c/o Fresenius Kabi USA, LLC, Three Corporate Dr., Lake Zurich, IL 60047.
ANDA 080420	Lidocaine Hydrochloride (HCl) Injection USP, 1%, 1.5%, and 2%.	Lyphomed, Inc., 2045 North Cornell Ave., Melrose Park, IL 60160.
ANDA 080421	Procaine HCl Injection USP, 1% and 2%	Do.
ANDA 083083	Lidocaine HCl Injection USP, 1% and 2%	Wyeth-Ayerst Laboratories, P.O. Box 8299, Philadelphia, PA 19101.
ANDA 083744	Lidocaine HCl Injection USP, 0.5%, 1%, 1.5%, and 2%	Tera Pharmaceuticals, Inc., 6920 Stanton Ave., Buena Park, CA 90621.
ANDA 083907	Lidocaine HCl With Epinephrine Injection USP	Do.
ANDA 084571	Lidocaine HCl Injection, 10 mg/20 mL and 10 mg/50 mL	Knoll Pharmaceuticals, 30 North Jefferson Rd., Whippany, NJ 07981.
ANDA 084572	Lidocaine HCl Injection, 20 mg/20 mL and 20 mg/50 mL	Do.
ANDA 084720	Lidocaine HCl and Epinephrine Injection USP, 2%; 0.01 mg/mL.	Naska Pharmacal Co., Inc., Riverview Rd., P.O. Box 898, Lincolnton, NC 28093.
ANDA 084732	Lidocaine HCl and Epinephrine Injection USP, 2%; 0.02 mg/mL.	Do.
ANDA 084947	Alphacaine (lidocaine) Ointment, 5%	Carlisle Laboratories, Inc., 404 Doughty Blvd., Inwood, NY 11696.
ANDA 085037	Lidocaine HCl Injection USP, 1% and 2%	Akorn, Inc., P.O. Box 1220, Decatur, IL 62525.
ANDA 085677	Cortisone Acetate Injectable Suspension USP, 25 mg/mL and 50 mg/mL.	Steris Laboratories, Inc., 620 North 51st Ave., Phoenix, AZ 85043.
ANDA 088051	Thalitone (chlorthalidone) Tablets USP, 25 mg	Casper Pharma LLC, 2 Tower Center Blvd., Suite 1101C, East Brunswick, NJ 08816.
ANDA 089688	Lidocaine HCl Topical Solution USP, 4%	Paco Research, Corp., 1705 Oak St., Lakewood, NJ 08701.
ANDA 091212	Lansoprazole Delayed-Release Capsules USP, 15 mg and 30 mg.	Krka, tovarna zdravil, d.d., Novo mesto, c/o KRKA USA, LLC.
ANDA 091377	Vancomycin HCl for Injection USP, EQ 500 mg base/vial and EQ 1gram (g) base/vial.	Xellia Pharmaceuticals ApS, c/o Xellia Pharmaceuticals USA, LLC, 8841 Wadford Dr., Raleigh, NC 27616.
ANDA 206243	Vancomycin HCl for Injection USP, EQ 5 g base/vial and EQ 10 g base/vial (Pharmacy Bulk Package).	Do.

Therefore, approval of the applications listed in the table, and all amendments and supplements thereto, is hereby withdrawn as of March 7, 2019. Introduction or delivery for introduction into interstate commerce of products without approved new drug applications violates section 301(a) and (d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(a) and (d)). Drug products that are listed in the table that are in inventory on March 7, 2019, may continue to be dispensed until the inventories have been depleted or the drug products have reached their expiration dates or otherwise become violative, whichever occurs first.

Dated: January 16, 2019.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2019–01129 Filed 2–4–19; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–1987–D–0240 (formerly 87D–0315)]

Neomycin Sulfate for Prescription Compounding; Withdrawal of Approval of One Abbreviated New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing approval of abbreviated new drug application (ANDA) 061579 for nonsterile neomycin sulfate powder for prescription compounding. The basis for the withdrawal is that the product is no longer considered safe as labeled due to clinical evidence that systemic exposure to neomycin sulfate can induce significant toxicity, including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade. The holder of this ANDA has waived its opportunity for a hearing.

DATES: Approval is withdrawn as of February 5, 2019.

FOR FURTHER INFORMATION CONTACT: Kate Greenwood, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6286, Silver Spring, MD 20993–0002, 240–402–1748.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of April 15, 1988, FDA published four documents arising out of the Agency's finding that systemic absorption of neomycin sulfate can induce significant toxicity, including ototoxicity (manifested as sensorineural hearing loss), nephrotoxicity, and neuromuscular blockade (see generally 53 FR 12644; 53 FR 12658; 53 FR 12662; and 53 FR 12664 (April 15, 1988)). Two of the four documents were issued under docket numbers FDA–1979–N–0220 and FDA–1987–D–0240 and related to nonsterile neomycin sulfate for prescription compounding.[1]

Under docket number FDA–1979–N–0220, FDA published a final rule amending the antibiotic drug

[1] These documents were originally assigned docket numbers 79N–0155, and 87D–0315. The numbers were changed to FDA–1979–N–0220 and FDA–1987–D–0240, respectively, as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. The other two documents were issued under docket number FDA–1979–N–0256 (formerly 79N–0151) and related to neomycin sulfate in sterile vials for parenteral use.

regulations governing the certification of nonsterile neomycin sulfate powder for prescription compounding (53 FR 12644). Based on its evaluation of the written and oral comments received on the proposed rule (44 FR 44180 (July 27, 1979)), and based on other information, FDA concluded that there was a favorable risk:benefit profile for orally administered neomycin sulfate preparations as adjunctive therapy for preoperative suppression of intestinal bacteria and for the treatment of hepatic coma. However, consistent with the findings published in the proposed rule, FDA concluded in the final rule that the risks of adverse reactions from the use of the product for wound irrigation resulted in systemic absorption and a resultant risk of adverse reactions that significantly outweighed any demonstrated benefits. Accordingly, the final rule amended the antibiotic drug regulations by changing the product name from ''neomycin sulfate for prescription compounding'' to ''neomycin sulfate for compounding oral products'' and by requiring package insert labeling to provide information concerning the appropriate uses of the product and to warn about the risks associated with inappropriate use.

Under docket number FDA–1987–D–0240, FDA proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)) withdrawing approval of six antibiotic drug applications and abbreviated antibiotic drug applications (AADAs) [2] for nonsterile neomycin sulfate for prescription compounding products unless the application holders submitted supplemental applications providing for a product name and labeling consistent with the revised name and labeling requirements described in the newly amended antibiotic certification regulations (53 FR 12662).[3] In the document, FDA announced the availability of guideline labeling for nonsterile neomycin sulfate for prescription compounding products that manufacturers could adopt to ensure that their labeling would be consistent with the labeling required by the revised antibiotic certification regulations. The proposed order was based on clinical or other experience, tests, or other scientific data that showed nonsterile neomycin sulfate was unsafe for use except when named ''Neomycin Sulfate for Compounding Oral Products'' and used in accordance with package insert labeling that provides information concerning appropriate uses and that warns about risks associated with inappropriate use. Under section 505 and the regulations promulgated at 21 CFR parts 310 and 314, the holders of the applications were given the opportunity for a hearing to show why approval should not be withdrawn. One application holder, Pharma-Tek, Inc. (Pharma-Tek), requested a hearing to challenge FDA's proposal to withdraw approval of its application, AADA 61–579. On December 6, 1988, FDA announced the withdrawal of approval of five of the six applications for nonsterile neomycin sulfate for prescription compounding for which the holders had not requested a hearing (53 FR 49231). The AADA for neomycin sulfate for prescription compounding, AADA 61–579, held by Pharma-Tek, was not withdrawn at that time because of the sponsor's pending hearing request. Today, this application corresponds to ANDA 061579 held by X-Gen Pharmaceuticals, Inc. (X-Gen).

X-Gen informed FDA by letter dated October 9, 2015, that it was withdrawing the hearing request previously filed on behalf of its predecessor Pharma-Tek concerning ANDA 061579. X-Gen also informed FDA that it waived the opportunity for a hearing and, under 21 CFR 314.150(d), X-Gen permitted the Agency to withdraw approval of ANDA 061579 for neomycin sulfate for prescription compounding.

For the reasons discussed in the document published in the **Federal Register** on April 15, 1988, under docket number FDA–1987–D–0240, the Director of FDA's Center for Drug Evaluation and Research finds that ANDA 061579 was withdrawn from sale for safety and effectiveness reasons (21 CFR 314.161(c)). The Director, under section 505(e) of the FD&C Act and under authority delegated to her by the Commissioner, also finds that new evidence of clinical experience, not contained in ANDA 061579 and not available at the time the application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that nonsterile neomycin sulfate for prescription compounding is not shown to be safe for use under the conditions of use upon the basis of which the application was approved (21 U.S.C. 355(e)). Therefore, approval of ANDA 061579 is hereby withdrawn.

Under 21 CFR 314.161(e) and 314.162(a)(2), FDA will remove ANDA 061579 from the list of drug products with effective approvals published in FDA's ''Approved Drug Products With Therapeutic Equivalence Evaluations.''

Dated: January 23, 2019.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2019–01131 Filed 2–4–19; 8:45 am]

BILLING CODE 4164–01–P

[2] The terms ''antibiotic drug applications'' and ''abbreviated antibiotic drug applications'' are no longer used. AADAs approved under section 507 of the FD&C Act on or before November 20, 1997, are deemed to have been approved under section 505(j) of the FD&C Act.

[3] This proposed regulatory action was necessary because the antibiotic drug certification regulations did not apply to products with applications in which FDA had approved alternative labeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–D–6702]

The Least Burdensome Provisions: Concept and Principles; Guidance for Industry and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance entitled ''The Least Burdensome Provisions: Concept and Principles.'' FDA utilizes a least burdensome approach to medical device regulation to eliminate unnecessary burdens that may delay the marketing of beneficial new products, while maintaining the statutory requirements for clearance and approval. This document describes the guiding principles and recommended approach for FDA staff and industry to facilitate consistent application of least burdensome principles to the activities pertaining to products meeting the statutory definition of a device regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

DATES: The announcement of the guidance is published in the **Federal Register** on February 5, 2019.

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are

APPENDIX 18:

Neo-Fradin
Oral Solution
Neomycin Sulfate Oral Solution, USP

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Oral Solution and other antibacterial drugs, Neomycin Sulfate Oral Solution should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

SYSTEMIC ABSORPTION OF NEOMYCIN OCCURS FOLLOWING ORAL ADMINISTRATION AND TOXIC REACTIONS MAY OCCUR. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with their use.

NEUROTOXICITY (INCLUDING OTOTOXICITY) AND NEPHROTOXICITY FOLLOWING THE ORAL USE OF NEOMYCIN SULFATE HAVE BEEN REPORTED, EVEN WHEN USED IN RECOMMENDED DOSES. THE POTENTIAL FOR NEPHROTOXICITY, PERMANENT BILATERAL AUDITORY OTOTOXICITY AND SOMETIMES VESTIBULAR TOXICITY IS PRESENT IN PATIENTS WITH NORMAL RENAL FUNCTION WHEN TREATED WITH HIGHER DOSES OF NEOMYCIN AND/OR FOR LONGER PERIODS THAN RECOMMENDED. Serial, vestibular, and audiometric tests, as well as tests of renal function, should be performed (especially in high risk patients).

THE RISK OF NEPHROTOXICITY AND OTOTOXICITY IS GREATER IN PATIENTS WITH IMPAIRED RENAL FUNCTION. Ototoxicity is often delayed in onset and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction and total or partial deafness may occur long after neomycin has been discontinued.

Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuromuscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena but mechanical respiratory assistance may be necessary.

Concurrent and/or sequential systemic, oral, or topical use of other aminoglycosides including paromomycin and other potentially nephrotoxic and/or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin, and viomycin should be avoided because the toxicity may be additive.

Other factors which increase the risk of toxicity are advanced age and dehydration.

The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.

DESCRIPTION
NEO-FRADIN Oral Solution for oral administration contains neomycin which is an antibiotic obtained from the metabolic products of the actinomycete Streptomyces fradiae. The pH range is 5.0 to 7.5. NEO-FRADIN Oral Solution is a clear orange solution with a cherry flavor. Each 5 mL of NEO-FRADIN Oral Solution contains 125 mg of neomycin sulfate (equivalent to 87.5 mg of neomycin).

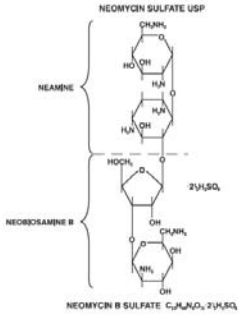
Inactive ingredients: benzoic acid, FD&C yellow no. 6, cherry flavor, glycerin, methylparaben, proplyparaben, sodium phosphate dibasic heptahydrate, sulfuric acid, diatomaceous earth, and purified water.

Sodium phosphate dibasic heptahydrate and sulfuric acid are used as pH adjusters.

The chemical name for Neomycin is: 0-2, 6-diamino-2, 6-dideoxy-α-D-lucopyranosyl-(1→3)- 0β-D-ribofuranosyl-(1→5)0-[2, 6-diamino-2, 6-dideoxy-α-D-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine.

Neomycin B is identical except that the -α-D-glucopyranosyl residue in the neobiosamine moiety is β-L-idopyranosly.

The molecular weight of Neomycin is 614.67. The structural formula is represented below:



CLINICAL PHARMACOLOGY
Neomycin sulfate is poorly absorbed from the gastrointestinal tract. The small absorbed fraction is rapidly distributed in the tissues and is excreted by the kidney in keeping with the degree of kidney function. The unabsorbed portion of the drug (approximately 97 percent) is eliminated unchanged in the feces.

Growth of most intestinal bacteria is rapidly suppressed following oral administration of neomycin sulfate, with the suppression persisting for 48-72 hours. Nonpathogenic yeasts and occasionally resistant strains of Enterobacter aerogenes (formerly Aerobacter aerogenes) replace the intestinal bacteria.

As with other aminoglycosides, the amount of systemically absorbed neomycin transferred to the tissues increases cumulatively with each repeated dose administered until a steady state is achieved. The kidney functions as the primary excretory path as well as the tissue binding site with the highest concentration found in renal cortex. With repeated dosings, progressive accumulation also occurs in the inner ear. Release of tissue bound neomycin occurs slowly over a period of several weeks after dosing has been discontinued.

Protein binding studies have shown that the degree of aminoglycoside protein binding is low and, depending upon the methods used for testing, this may be between 0 and 30 percent.

Microbiology
In vitro tests have demonstrated that neomycin is bactericidal and acts by inhibiting the synthesis of protein in susceptible bacterial cells. It is effective primarily against gram-negative bacilli but does have some activity against gram-positive organisms. Neomycin is active in vitro against Escherichia coli and the Klebsiella-Enterobacter group. Neomycin is not active against anaerobic bowel flora.

If susceptibility testing is needed, using a 30 mcg disc, organisms producing zones of 16 mm or greater are considered susceptible. Resistant organisms produce zones of 13 mm or less. Zones greater than 13 mm and less than 16 mm indicate intermediate susceptibility.

INDICATIONS AND USAGE
Hepatic coma (portal-systemic encephalopathy)
Neomycin sulfate has been shown to be effective adjunctive therapy in hepatic coma by reduction of the ammonia forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurologic improvement.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Oral Solution and other antibacterial drugs, Neomycin Sulfate Oral Solution should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
Neomycin sulfate oral preparations are contraindicated in the presence of intestinal obstruction and in individuals with a history of hypersensitivity to the drug.

Patients with a history of hypersensitivity or serious toxic reaction to other aminoglycosides may have a cross-sensitivity to neomycin.

Neomycin sulfate oral solution is contraindicated in patients with inflammatory or ulcerative gastrointestinal disease because of the potential for enhanced gastrointestinal absorption of neomycin.

WARNINGS
(see boxed WARNINGS)
Additional manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions.

The risk of hearing loss continues after drug withdrawal.

Aminoglycosides can cause fetal harm when administered to a pregnant woman.

Aminoglycoside antibiotics cross the placenta and there have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to fetus or newborn have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Animal reproduction studies of neomycin have not been conducted. If neomycin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS
General
Prescribing Neomycin Sulfate Oral Solution in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotics, use of oral neomycin may result in overgrowth of non-susceptible organisms, particularly fungi. If this occurs, appropriate therapy should be instituted.

Neomycin is quickly and almost totally absorbed from body surfaces (except the urinary bladder) after local irrigation and when applied topically in association with surgical procedures. Delayed-onset, irreversible deafness, renal failure, and death due to neuromuscular blockade (regardless of the status of renal function) have been reported following irrigation of both small and large surgical fields with minute quantities of neomycin.

Cross-allergenicity among aminoglycosides has been demonstrated.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

Small amounts of orally administered neomycin are absorbed through intact intestinal mucosa.

There have been many reports in the literature of nephrotoxicity and/or ototoxicity with the oral use of neomycin. If renal insufficiency develops during oral therapy, consideration should be given to reducing the drug dosage or discontinuing therapy.

An oral neomycin dose of 12 grams per day produces a malabsorption syndrome for a variety of substances including fat, nitrogen, cholesterol, carotene, glucose, xylose, lactose, sodium, calcium, cyanocobalamin and iron.

Oral administered neomycin increases fecal bile acid excretion and reduces intestinal lactase activity.

Information for Patients
Patients should be counseled that antibacterial drugs including Neomycin Sulfate Oral Solution should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Neomycin Sulfate Oral Solution is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Neomycin Sulfate Oral Solution or other antibacterial drugs in the future.

Before administering the drug, patients or members of their families should be informed of possible toxic effects of the eighth nerve. The possibility of acute toxicity increases in premature infants and neonates.

Laboratory Tests
Patients with renal insufficiency may develop toxic neomycin blood levels unless doses are properly regulated. If renal insufficiency develops during treatment, the dosage should be reduced or the antibiotic discontinued. To avoid nephrotoxicity and eighth nerve damage associated with high doses and prolonged treatment, the following should be performed prior to and periodically during therapy: urinalysis for increased excretion of protein, decreased specific gravity, casts and cells; renal function tests such as serum creatinine, BUN or creatinine clearance; tests of the vestibulocochlearis nerve (eighth cranial nerve) function.

Serial, vestibular and audiometric tests should be performed (especially in high risk patients). Since elderly patients may have reduced renal function which may not be evident in the results of routine screening tests such as BUN or serum creatinine, a creatinine clearance determination may be more useful.

Drug Interactions
Caution should be taken in concurrent or serial use of other neurotoxic and/or nephrotoxic drugs because of possible enhancement of the nephrotoxicity and/or ototoxicity of neomycin (see boxed WARNINGS).

Caution should also be taken in concurrent or serial use of other aminoglycosides and polymyxins because they may enhance neomycin's nephrotoxicity and/or ototoxicity and potentiate neomycin's neuromuscular blocking effects.

Oral neomycin inhibits the gastrointestinal absorption of penicillin V, oral vitamin B-12, methotrexate and 5-fluorourcil. The gastrointestinal absorption of digoxin also appears to be inhibited. Therefore, digoxin serum levels should be monitored.

Oral neomycin may enhance the effect of coumarin in anticoagulants by decreasing vitamin K availability.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed with neomycin to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy Category D (see WARNINGS section)
Nursing Mothers
It is not known whether neomycin is excreted in human milk but it has been shown to be excreted in cow milk following a single intramuscular injection. Other aminoglycosides have been shown to be excreted in human milk. Because of the potential for serious adverse reactions from the aminoglycosides in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and efficacy of oral neomycin in patients less than eighteen years of age have not been established. If treatment of a patient less than eighteen years of age is necessary, neomycin should be used with caution and the period of treatment should not exceed three weeks because of the absorption from the gastrointestinal tract.

ADVERSE REACTIONS
The most common adverse reactions to oral neomycin are nausea, vomiting, and diarrhea. The "Malabsorption Syndrome" characterized by increased fecal fat, decreased serum carotene and fall in xylose absorption has been reported with prolonged therapy. Nephrotoxicity, ototoxicity, and neuromuscular blockage have been reported (see boxed WARNINGS and PRECAUTIONS section).

OVERDOSAGE
Because of low absorption, it is unlikely that acute overdosage would occur with oral neomycin. However, prolonged administration could result in sufficient systemic drug levels to produce neurotoxicity, ototoxicity, and/or nephrotoxicity.

Hemodialysis will remove neomycin from the blood.

DOSAGE AND ADMINISTRATION
To minimize the risk of toxicity use the lowest possible dose and the shortest possible treatment period to control the condition. Treatment for periods longer than two weeks is not recommended.

Hepatic coma

For use as an adjunct in the management of hepatic coma, the recommended dose is 4-12 grams per day given in the following regimen:

1. Withdraw protein from diet. Avoid use of diuretic agents.
2. Give supportive therapy including blood products, as indicated.
3. Give NEO-FRADIN Oral Solution in doses of four to twelve grams of neomycin sulfate per day in divided doses.

   Treatment should be continued over a period of five to six days during which time protein should be returned incrementally to the diet.
4. If less potentially toxic drugs cannot be used for chronic hepatic insufficiency, neomycin sulfate in doses of up to four grams daily may be necessary. The risks for the development of neomycin induced toxicity progressively increase when the treatment must be extended to preserve the life of a patient with hepatic encephalopathy who has failed to fully respond. Frequent periodic monitoring of these patients to ascertain the presence of drug toxicity is mandatory (see PRECAUTIONS). Also, neomycin serum concentrations should be monitored to avoid potentially toxic levels. The benefits to the patient should be weighed against the risks of nephrotoxicity, permanent ototoxicity and neuromuscular blockade following the accumulation of neomycin in the tissues.

HOW SUPPLIED
NEO-FRADIN Oral Solution is available as a clear orange solution with a cherry flavor in 16 fl. oz bottles containing 125 mg of neomycin sulfate (equivalent to 87.5 mg of neomycin) per five mL.

NDC 39822-0330-5 for 16 fl. oz.

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Manufactured for:
X-Gen Pharmaceuticals, Inc.
Revised November 2011

APPENDIX 19:

NEOMYCIN SULFATE- neomycin sulfate tablet
Teva Pharmaceuticals USA Inc

NEOMYCIN SULFATE TABLETS USP, 500 MG
1177
Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Tablets USP and other antibacterial drugs, Neomycin Sulfate Tablets USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNINGS

SYSTEMIC ABSORPTION OF NEOMYCIN OCCURS FOLLOWING ORAL ADMINISTRATION AND TOXIC REACTIONS MAY OCCUR. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with their use. NEUROTOXICITY (INCLUDING OTOTOXICITY) AND NEPHROTOXICITY FOLLOWING THE ORAL USE OF NEOMYCIN SULFATE HAVE BEEN REPORTED, EVEN WHEN USED IN RECOMMENDED DOSES. THE POTENTIAL FOR NEPHROTOXICITY, PERMANENT BILATERAL AUDITORY OTOTOXICITY AND SOMETIMES VESTIBULAR TOXICITY IS PRESENT IN PATIENTS WITH NORMAL RENAL FUNCTION WHEN TREATED WITH HIGHER DOSES OF NEOMYCIN AND/OR FOR LONGER PERIODS THAN RECOMMENDED. Serial, vestibular and audiometric tests, as well as tests of renal function, should be performed (especially in high-risk patients). THE RISK OF NEPHROTOXICITY AND OTOTOXICITY IS GREATER IN PATIENTS WITH IMPAIRED RENAL FUNCTION. Ototoxicity is often delayed in onset and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction and total or partial deafness may occur long after neomycin has been discontinued.

Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuromuscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena but mechanical respiratory assistance may be necessary.

Concurrent and/or sequential systemic, oral or topical use of other aminoglycosides, including paromomycin and other potentially nephrotoxic and/or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin and viomycin, should be avoided because the toxicity may be additive.

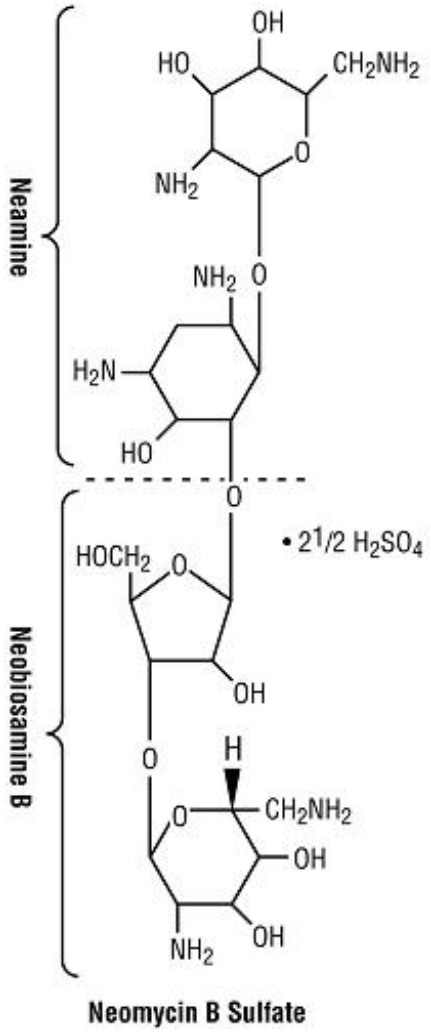
Other factors which increase the risk of toxicity are advanced age and dehydration.

The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.

DESCRIPTION

Neomycin Sulfate Tablets, USP, for oral administration, contain neomycin which is an antibiotic obtained from the metabolic products of the actinomycete *Streptomyces fradiae*. Structurally, neomycin

sulfate may be represented as follows:



Neomycin B Sulfate

$C_{23}H_{46}N_6O_{13}\cdot 2½\ H_2SO_4$ MW 614.67

Chemically, it is *0*-2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→3)-*0*-β-D-ribofuranosyl-(1→5)-*0*-[2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine. Neomycin B is identical except that the a-D-glucopyranosyl residue in the neobiosamine moiety is β-L-idopyranosyl.

Inactive Ingredients: Calcium Stearate, Povidone.

CLINICAL PHARMACOLOGY

Neomycin sulfate is poorly absorbed from the normal gastrointestinal tract. The small absorbed fraction is rapidly distributed in the tissues and is excreted by the kidney in keeping with the degree of kidney function. The unabsorbed portion of the drug (approximately 97%) is eliminated unchanged in the feces.

Growth of most intestinal bacteria is rapidly suppressed following oral administration of neomycin sulfate, with the suppression persisting for 48 to 72 hours. Nonpathogenic yeasts and occasionally resistant strains of *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*) replace the intestinal bacteria.

As with other aminoglycosides, the amount of systemically absorbed neomycin transferred to the tissues increases cumulatively with each repeated dose administered until a steady state is achieved. The kidney functions as the primary excretory path as well as the tissue binding site, with the highest

concentration found in the renal cortex. With repeated dosings, progressive accumulation also occurs in the inner ear. Release of tissue-bound neomycin occurs slowly over a period of several weeks after dosing has been discontinued.

Protein binding studies have shown that the degree of aminoglycoside protein binding is low and, depending upon the methods used for testing, this may be between 0% and 30%.

Microbiology

In vitro tests have demonstrated that neomycin is bactericidal and acts by inhibiting the synthesis of protein in susceptible bacterial cells. It is effective primarily against gram-negative bacilli but does have some activity against gram-positive organisms. Neomycin is active *in vitro* against *Escherichia coli* and the *Klebsiella-Enterobacter* group. Neomycin is not active against anaerobic bowel flora.

If susceptibility testing is needed, using a 30 mcg disc, organisms producing zones of 16 mm or greater are considered susceptible. Resistant organisms produce zones of 13 mm or less. Zones greater than 13 mm and less than 16 mm indicate intermediate susceptibility.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Tablets USP and other antibacterial drugs, Neomycin Sulfate Tablets USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Suppression of intestinal bacteria

Neomycin sulfate tablets are indicated as adjunctive therapy as part of a regimen for the suppression of the normal bacterial flora of the bowel, eg, preoperative preparation of the bowel. It is given concomitantly with erythromycin enteric-coated base (see **DOSAGE AND ADMINISTRATION**).

Hepatic coma (portal-systemic encephalopathy)

Neomycin sulfate has been shown to be effective adjunctive therapy in hepatic coma by reduction of the ammonia-forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurologic improvement.

CONTRAINDICATIONS

Neomycin sulfate oral preparations are contraindicated in the presence of intestinal obstruction and in individuals with a history of hypersensitivity to the drug.

Patients with a history of hypersensitivity or serious toxic reaction to other aminoglycosides may have a cross-sensitivity to neomycin.

Neomycin sulfate oral preparations are contraindicated in patients with inflammatory or ulcerative gastrointestinal disease because of the potential for enhanced gastrointestinal absorption of neomycin.

WARNINGS (see BOXED WARNINGS)

Additional manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions.

The risk of hearing loss continues after drug withdrawal.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycoside

antibiotics cross the placenta and there have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to fetus or newborn have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Animal reproduction studies of neomycin have not been conducted. If neomycin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

Prescribing Neomycin Sulfate Tablets USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotics, use of oral neomycin may result in overgrowth of nonsusceptible organisms, particularly fungi. If this occurs, appropriate therapy should be instituted.

Neomycin is quickly and almost totally absorbed from body surfaces (except the urinary bladder) after local irrigation and when applied topically in association with surgical procedures. Delayed-onset irreversible deafness, renal failure and death due to neuromuscular blockade (regardless of the status of renal function) have been reported following irrigation of both small and large surgical fields with minute quantities of neomycin.

Cross-allergenicity among amino-glycosides has been demonstrated.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

Small amounts of orally administered neomycin are absorbed through intact intestinal mucosa.

There have been many reports in the literature of nephrotoxicity and/or ototoxicity with oral use of neomycin. If renal insufficiency develops during oral therapy, consideration should be given to reducing the drug dosage or discontinuing therapy.

An oral neomycin dose of 12 grams per day produces a malabsorption syndrome for a variety of substances, including fat, nitrogen, cholesterol, carotene, glucose, xylose, lactose, sodium, calcium, cyanocobalamin and iron.

Orally administered neomycin increases fecal bile acid excretion and reduces intestinal lactase activity.

Information for the patient

Patients should be counseled that antibacterial drugs including Neomycin Sulfate Tablets USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Neomycin Sulfate Tablets USP are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Neomycin Sulfate Tablets USP or other antibacterial drugs in the future.

Before administering the drug, patients or members of their families should be informed of possible toxic effects on the eighth nerve. The possibility of acute toxicity increases in premature infants and neonates.

Laboratory tests

Patients with renal insufficiency may develop toxic neomycin blood levels unless doses are properly regulated. If renal insufficiency develops during treatment, the dosage should be reduced or the antibiotic discontinued. To avoid nephrotoxicity and eighth nerve damage associated with high doses and prolonged treatment, the following should be performed prior to and periodically during therapy: urinalysis for increased excretion of protein, decreased specific gravity, casts and cells; renal function tests such as serum creatinine, BUN or creatinine clearance; tests of the vestibulocochlearis nerve (eighth cranial nerve) function.

Serial, vestibular and audiometric tests should be performed (especially in high-risk patients). Since elderly patients may have reduced renal function which may not be evident in the results of routine screening tests such as BUN or serum creatinine, a creatinine clearance determination may be more useful.

Drug interactions

Caution should be taken in concurrent or serial use of other neurotoxic and/or nephrotoxic drugs because of possible enhancement of the nephrotoxicity and/or ototoxicity of neomycin (see boxed **WARNINGS**).

Caution should also be taken in concurrent or serial use of other amino-glycosides and polymyxins because they may enhance neomycin's nephrotoxicity and/or ototoxicity and potentiate neomycin sulfate's neuromuscular blocking effects.

Oral neomycin inhibits the gastrointestinal absorption of penicillin V, oral vitamin B-12, methotrexate and 5-fluorouracil. The gastrointestinal absorption of digoxin also appears to be inhibited. Therefore, digoxin serum levels should be monitored.

Oral neomycin sulfate may enhance the effect of coumarin in anticoagulants by decreasing vitamin K availability.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term animal studies have been performed with neomycin sulfate to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy Category D

(See **Warnings** section.)

Nursing Mothers

It is not known whether neomycin is excreted in human milk, but it has been shown to be excreted in cow milk following a single intramuscular injection. Other aminoglycosides have been shown to be excreted in human milk. Because of the potential for serious adverse reactions from the aminoglycosides in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of oral neomycin sulfate in patients less than 18 years of age have not been established. If treatment of a patient less than 18 years of age is necessary, neomycin should be used with caution and the period of treatment should not exceed two weeks because of absorption from the gastrointestinal tract.

ADVERSE REACTIONS

The most common adverse reactions to oral neomycin sulfate are nausea, vomiting and diarrhea. The "Malabsorption Syndrome" characterized by increased fecal fat, decreased serum carotene and fall in xylose absorption has been reported with prolonged therapy. Nephrotoxicity, ototoxicity and

neuromuscular blockage have been reported (see boxed **WARNINGS** and **PRECAUTIONS** sections).

OVERDOSAGE

Because of low absorption, it is unlikely that acute overdosage would occur with oral neomycin sulfate. However, prolonged administration could result in sufficient systemic drug levels to produce neurotoxicity, ototoxicity and/or nephrotoxicity.

Hemodialysis will remove neomycin sulfate from the blood.

DOSAGE AND ADMINISTRATION

To minimize the risk of toxicity, use the lowest possible dose and the shortest possible treatment period to control the condition. Treatment for periods longer than two weeks is not recommended.

Hepatic coma

For use as an adjunct in the management of hepatic coma, the recommended dose is 4 to 12 grams per day given in the following regimen:

1. Withdraw protein from diet. Avoid use of diuretic agents.
2. Give supportive therapy, including blood products, as indicated.
3. Give neomycin sulfate tablets in doses of 4 to 12 grams of neomycin sulfate per day (eight to 24 tablets) in divided doses. Treatment should be continued over a period of five to six days, during which time protein should be returned incrementally to the diet.
4. If less potentially toxic drugs cannot be used for chronic hepatic insufficiency, neomycin in doses of up to four grams daily (eight tablets per day) may be necessary. The risk for the development of neomycin-induced toxicity progressively increases when treatment must be extended to preserve the life of a patient with hepatic encephalopathy who has failed to fully respond. Frequent periodic monitoring of these patients to ascertain the presence of drug toxicity is mandatory (see **PRECAUTIONS**). Also, neomycin serum concentrations should be monitored to avoid potentially toxic levels. The benefits to the patient should be weighed against the risks of nephrotoxicity, permanent ototoxicity and neuromuscular blockade following the accumulation of neomycin in the tissues.

Preoperative Prophylaxis for Elective Colorectal Surgery

Listed below is an example of a recommended bowel preparation regimen. A proposed surgery time of 8:00 a.m. has been used.

Pre-op Day 3: Minimum residue or clear liquid diet. Bisacodyl, 1 tablet orally at 6:00 p.m.

Pre-op Day 2: Minimum residue or clear liquid diet. Magnesium sulfate, 30 mL, 50% solution (15 g) orally at 10:00 a.m., 2:00 p.m., and 6:00 p.m. Enema at 7:00 p.m. and 8:00 p.m.

Pre-op Day 1: Clear liquid diet. Supplemental (IV) fluids as needed. Magnesium sulfate, 30 mL, 50% solution (15 g) orally at 10:00 a.m., and 2:00 p.m. Neomycin sulfate (1 g) and erythromycin base (1 g) orally at 1:00 p.m., 2:00 p.m. and 11:00 p.m. No enema.

Day of Operation: Patient evacuates rectum at 6:30 a.m. for scheduled operation at 8:00 a.m.

HOW SUPPLIED

Neomycin Sulfate Tablets USP, 500 mg (equivalent to 350 mg of neomycin base per tablet) are available as round, off-white, unscored tablets, debossed “93” and “1177”, in bottles of 100 tablets (NDC 0093-1177-01).

Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP).

Dispense in tight containers as defined in the USP/NF.

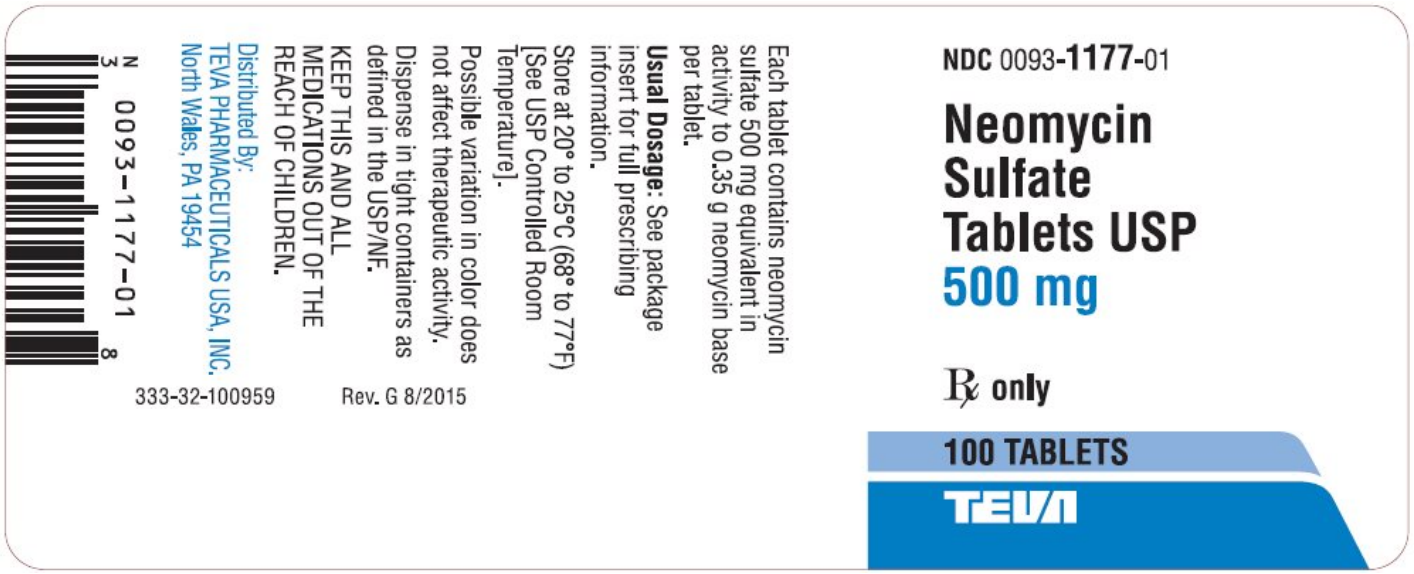
Distributed By:

TEVA PHARMACEUTICALS USA, INC.

North Wales, PA 19454

Rev. E 8/2015

Package/Label Display Panel



Neomycin Sulfate Tablets USP 500 mg 100s Label Text

NDC 0093-**1177**-01

NEOMYCIN

SULFATE

Tablets, USP

500 mg

Rx only

100 TABLETS

TEVA

NEOMYCIN SULFATE

neomycin sulfate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0093-1177
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NEOMYCIN SULFATE (UNII: 057Y626693) (NEOMYCIN - UNII:I16QD7X297)	NEOMYCIN	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM STEARATE (UNII: 776XM7047L)	
POVIDONE K29/32 (UNII: 390RMW2PEQ)	

Product Characteristics			
Color	WHITE (off-white)	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	93;1177
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0093-1177-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/30/1990	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA060304	09/30/1990	

Labeler - Teva Pharmaceuticals USA Inc (001627975)

Revised: 11/2015 Teva Pharmaceuticals USA Inc

APPENDIX 20:

NEOMYCIN AND POLYMYXIN B SULFATES - neomycin sulfate and polymyxin b sulfate irrigant
Watson Laboratories, Inc.

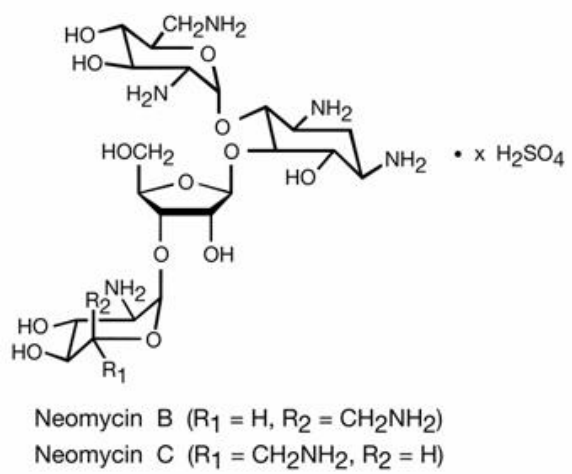
NEOMYCIN AND POLYMYXIN B SULFATES
SOLUTION FOR IRRIGATION USP
NOT FOR INJECTION
Rx only

695308010591*B1

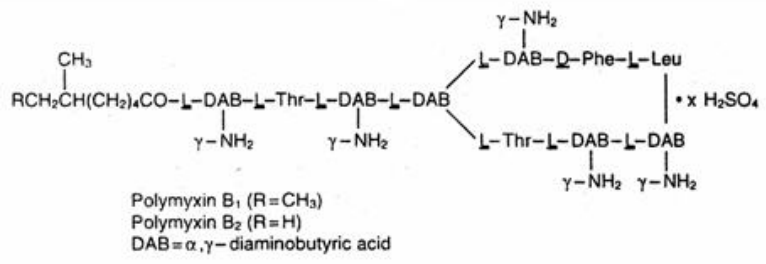
DESCRIPTION

Neomycin and Polymyxin B Sulfates Solution for Irrigation is a concentrated sterile antibiotic solution to be diluted for urinary bladder irrigation. Each mL contains neomycin sulfate equivalent to 40 mg neomycin base, 200,000 units polymyxin B sulfate, and water for injection.

Neomycin sulfate, an antibiotic of the aminoglycoside group, is the sulfate salt of neomycin B and C produced by Streptomyces fradiae. It has a potency equivalent to not less than 600µg of neomycin per mg. The structural formulae are:



Polymyxin B sulfate, a polypeptide antibiotic, is the sulfate salt of polymyxin B1 and B2 produced by the growth of Bacillus polymyxa. It has a potency of not less than 6,000 polymyxin B units per mg. The structural formulae are:



CLINICAL PHARMACOLOGY

After prophylactic irrigation of the intact urinary bladder, neomycin and polymyxin B are absorbed in clinically insignificant quantities. A neomycin serum level of 0.1 µg/mL was observed in three of 33 patients receiving the rinse solution. This level is well below that which has been associated with neomycin-induced toxicity.

When used topically, polymyxin B sulfate and neomycin are rarely irritating.

Microbiology: The prepared Neomycin and Polymyxin B Sulfates Solution for Irrigation solution is bactericidal. The aminoglycosides act by inhibiting normal protein synthesis in susceptible microorganisms. Polymyxins increase the

permeability of bacterial cell wall membranes. The solution is active in vitro against

Escherichia coli
Staphylococcus aureus
Haemophilus influenzae
Klebsiella and Enterobacter species
Neisseria species, and
Pseudomonas aeruginosa.

It is not active in vitro against Serratia marcescens and streptococci.

Bacterial resistance may develop following the use of the antibiotics in the catheter-rinse solution.

INDICATIONS AND USAGE

Neomycin and Polymyxin B Sulfates Solution for Irrigation is indicated for short-term use (up to 10 days) as a continuous irrigant or rinse in the urinary bladder of abacteriuric patients to help prevent bacteriuria and gram-negative rod septicemia associated with the use of indwelling catheters.

Since organisms gain entrance to the bladder by way of, through, and around the catheter, significant bacteriuria is induced by bacterial multiplication in the bladder urine, in the mucoid film often present between catheter and urethra, and in other sites. Urinary tract infection may result from the repeated presence in the urine of large numbers of pathogenic bacteria. The use of closed systems with indwelling catheters has been shown to reduce the risk of infection. A three-way closed catheter system with constant neomycin-polymyxin B bladder rinse is indicated to prevent the development of infection while using indwelling catheters.

If uropathogens are isolated, they should be identified and tested for susceptibility so that appropriate antimicrobial therapy for systemic use can be initiated.

CONTRAINDICATIONS

Hypersensitivity to neomycin, the polymyxins, or any ingredient in the solution is a contraindication to its use. A history of hypersensitivity or serious toxic reaction to an aminoglycoside may also contraindicate the use of any other aminoglycoside because of the known cross-sensitivity of patients to drugs of this class.

WARNINGS

PROPHYLACTIC BLADDER CARE WITH NEOMYCIN AND POLYMYXIN B SULFATES SOLUTION FOR IRRIGATION SHOULD NOT BE GIVEN WHERE THERE IS A POSSIBILITY OF SYSTEMIC ABSORPTION. NEOMYCIN AND POLYMYXIN B SULFATES SOLUTION FOR IRRIGATION SHOULD NOT BE USED FOR IRRIGATION OTHER THAN FOR THE URINARY BLADDER. Systemic absorption after topical application of neomycin to open wounds, burns, and granulating surfaces is significant and serum concentrations comparable to and often higher than those attained following oral and parenteral therapy have been reported. Absorption of neomycin from the denuded bladder surface has been reported.

However, the likelihood of toxicity following topical irrigation of the intact urinary bladder with Neomycin and Polymyxin B Sulfates Solution for Irrigation is low since no appreciable amounts of these antibiotics enter the systemic circulation by this route if irrigation does not exceed 10 days.

Neomycin and Polymyxin B Sulfates Solution for Irrigation is intended for continuous prophylactic irrigation of the lumen of the intact urinary bladder of patients with indwelling catheters. Patients should be under constant supervision by a physician. Irrigation should be avoided in patients with defects in the bladder mucosa or bladder wall, such as vesical rupture, or in association with operative procedures on the bladder wall, because of the risk of toxicity due to systemic absorption following diffusion into absorptive tissues and spaces. When absorbed, neomycin and polymyxin B are nephrotoxic antibiotics, and the nephrotoxic potentials are additive. In addition, both antibiotics, when absorbed, are neurotoxins: neomycin can destroy fibers of the acoustic nerve causing permanent bilateral deafness; neomycin and polymyxin B are additive in their neuromuscular blocking effects, not only in terms of potency and duration, but also in terms of characteristics of the blocks produced.

Aminoglycosides, when absorbed, can cause fetal harm when administered to a pregnant woman. Aminoglycoside antibiotics cross the placenta and there have been several reports of total, irreversible, bilateral, congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. If Neomycin and Polymyxin B Sulfates Solution for Irrigation is used during pregnancy, the patient should be apprised of the potential hazard to the fetus (SeePRECAUTIONS).

PRECAUTIONS

General

Ototoxicity, nephrotoxicity, and neuromuscular blockade may occur if Neomycin and Polymyxin B Sulfates Solution for Irrigation ingredients are systemically absorbed (SeeWARNINGS). Absorption of neomycin from the denuded bladder surface has been reported. Patients with impaired renal function, infants, dehydrated patients, elderly patients, and patients receiving high doses of prolonged treatment are especially at risk for the development of toxicity.

Irrigation of the bladder with Neomycin and Polymyxin B Sulfates Solution for Irrigation may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. The safety and effectiveness of the preparation for use in the care of patients with recent lower urinary tract surgery have not been established.

Urine specimens should be collected during prophylactic bladder care for urinalysis, culture, and susceptibility testing. Positive cultures suggest the presence of organisms which are resistant to the bladder rinse antibiotics.

Pregnancy

Teratogenic Effects

Pregnancy Category D. SeeWARNINGS section.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Neomycin occasionally causes skin sensitization when applied topically; however, topical application to mucus membranes rarely results in local or systemic hypersensitivity reactions.

Irritation of the urinary bladder mucosa has been reported.

Signs of ototoxicity and nephrotoxicity have been reported following parenteral use of these drugs and following the oral and topical use of neomycin (SeeWARNINGS).

DOSAGE AND ADMINISTRATION

This preparation is specifically designed for use with “three-way” catheters or with other catheter systems permitting continuous irrigation of the urinary bladder. The usual irrigation dose is one 1-mL ampule a day for up to 10 days.

Using strict aseptic techniques, the contents of one 1-mL ampule of Neomycin and Polymyxin B Sulfates Solution for Irrigation should be added to a 1,000-mL container of isotonic saline solution. This container should then be connected to the inflow lumen of the “three-way” catheter which has been inserted with full aseptic precautions; use of a sterile lubricant is recommended during insertion of the catheter. The outflow lumen should be connected, via a sterile disposable plastic tube, to a disposable plastic collection bag. Stringent procedures, such as taping the inflow and outflow junction at the catheter, should be observed when necessary to insure the junctional integrity of the system.

For most patients, the inflow rate of the 1,000-mL saline solution of neomycin and polymyxin B should be adjusted to a slow drip to deliver about 1,000 mL every 24 hours. If the patient’s urine output exceeds 2 liters per day, it is recommended that the inflow rate be adjusted to deliver 2,000 mL of the solution in a 24 hour period.

It is important that the rinse of the bladder be continuous; the inflow or rinse solution should not be interrupted for more than a few minutes.

Preparation of the irrigation solution should be performed with strict aseptic techniques. The prepared solution should be stored at 4° C, and should be used within 48 hours following preparation to reduce the risk of contamination with resistant microorganisms.

HOW SUPPLIED

Sterile Neomycin and Polymyxin B Sulfate Solution for Irrigation is available in 1 mL ampules, cartons of 10 and 50.

Refrigerate at 2°-8° C (36°-46° F).

Literature Revised: January 2008

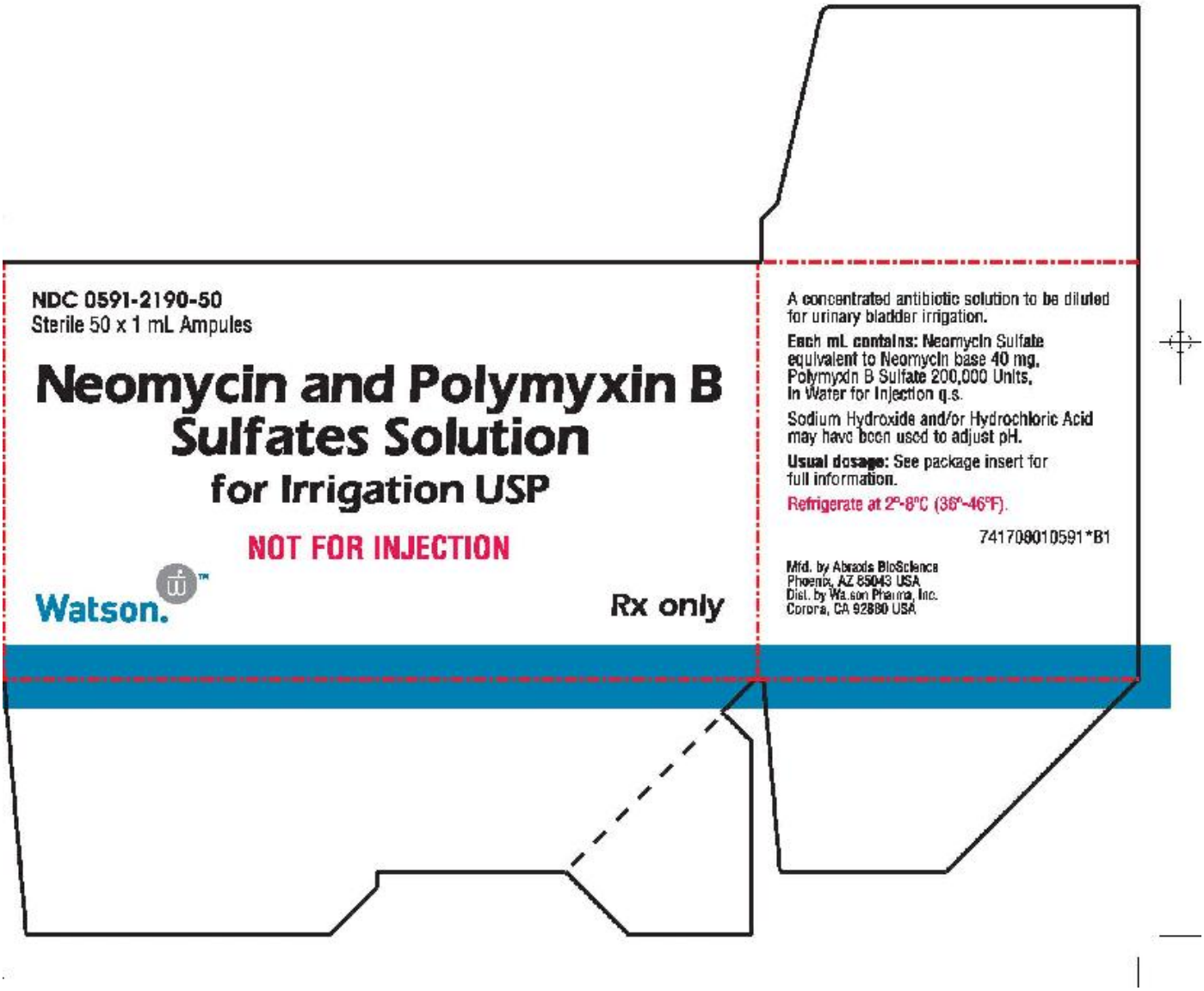
Product No.: 0801-81

Mfd. by Abraxis BioScience
Phoenix, AZ 85043 USA

Dist. by Watson Pharma, Inc.
Corona, CA 92880 USA

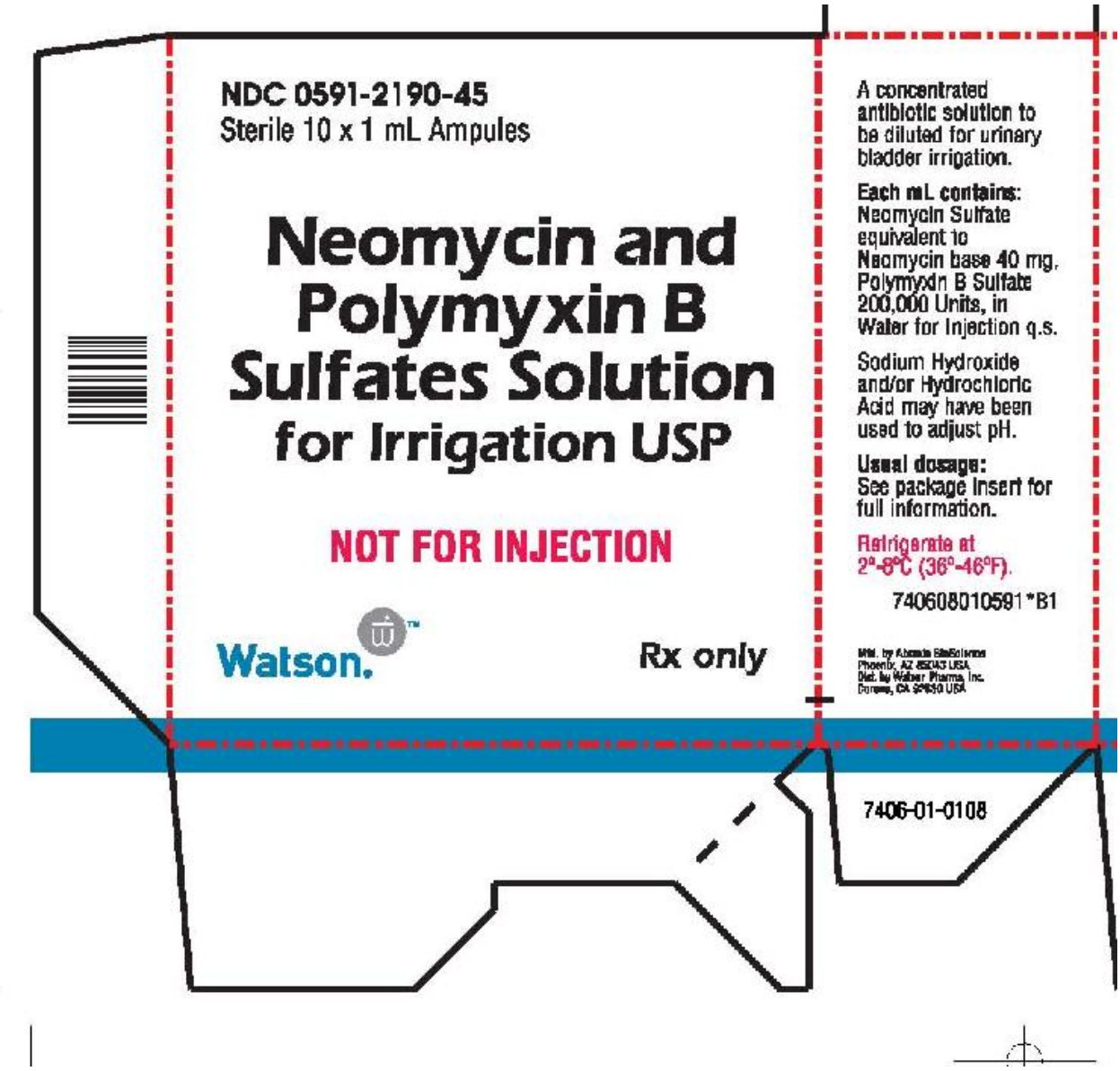
PRINCIPAL DISPLAY PANEL

0591-2190-50
Sterile 50 x 1 mL Ampules
Neomycin and Polymyxin B
Sulfates Solution
for Irrigation USP
NOT FOR INJECTION
Rx Only



PRINCIPAL DISPLAY PANEL

0591-2190-45
Sterile 10 x 1 mL Ampules
Neomycin and Polymyxin B
Sulfates Solution
for Irrigation USP
NOT FOR INJECTION
Rx Only



NEOMYCIN AND POLYMYXIN B SULFATES
neomycin and polymyxin b sulfates irrigant

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	NDC Product Code (Source)	0591-2190
Route of Administration	IRRIGATION	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NEOMYCIN SULFATE (NEOMYCIN)	NEOMYCIN SULFATE	40 mg in 1 mL
POLYMYXIN B SULFATE (POLYMYXIN B)	POLYMYXIN B SULFATE	200000 [USP'U] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER	

Product Characteristics

Color	Score
Shape	Size
Flavor	Imprint Code

Contains

Packaging

#	NDC	Package Description	Multilevel Packaging
1	0591-2190-45	10 AMPULE In 1 CARTON	contains a AMPULE
1		1 mL In 1 AMPULE	This package is contained within the CARTON (0591-2190-45)
2	0591-2190-50	50 AMPULE In 1 CARTON	contains a AMPULE
2		1 mL In 1 AMPULE	This package is contained within the CARTON (0591-2190-50)

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA062664	04/08/1986	

Labeler - Watson Laboratories, Inc. (023932721)

Establishment

Name	Address	ID/FEI	Operations
Abraxis BioScience, LLC - Phoenix		831637074	MANUFACTURE

Revised: 08/2010Watson Laboratories, Inc.