

# **FDA Briefing Document**

## **Pharmacy Compounding Advisory Committee (PCAC) Meeting**

**November 3, 2016**

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.

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## **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).

The Drug Quality and Security Act added a new section 503B to the FD&C Act, under which a compounder can elect to register as an outsourcing facility. Outsourcing facilities, as defined in section 503B of the FD&C Act, are facilities that meet certain conditions described in section 503B, including registration with FDA as an outsourcing facility. If these conditions are satisfied, a drug product compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from three sections of the FD&C Act: (1) Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); (2) section 505 (concerning the approval of human drug products under NDAs or ANDAs); and (3) section 582 (concerning the requirements of the Drug Supply Chain Security Act). Outsourcing facilities remain subject to CGMP requirements. Outsourcing facilities can compound drugs with or without receiving patient specific prescriptions or orders.

### **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 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 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 may be used to compound drug products under section 503A of the FD&C Act (503A Bulks List). As discussed at the February 2015 PCAC meeting, in the July 2014 *Federal Register* notice (79 FR 37747) (July 2, 2014) soliciting nominations for the section 503A Bulks List, FDA proposed the following criteria to evaluate the nominated substances:

- (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.

No single one of these criteria is dispositive. Rather, the agency is considering each criterion in the context of the others and balancing them, on a substance-by-substance basis, in deciding whether a particular substance is appropriate for inclusion on the list.

## **B. Drug Products and Categories of Drug Products that Present Demonstrable Difficulties for Compounding**

Both sections 503A and 503B of the FD&C Act require compounded drug products to satisfy several conditions to qualify for the statutory exemptions from the FD&C Act listed in each section.

One of the conditions for the exemptions under section 503A is that the compounded drug product is not a drug product that “presents demonstrable difficulties for

compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3).

Similarly, one of the conditions for the exemptions under section 503B is that the compounded drug product “is not identified (directly or as part of a category of drugs) on a list published by the Secretary . . . of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or “is compounded in accordance with all applicable conditions identified . . . as conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

FDA is considering those substances nominated for inclusion on the list of drug products and categories of drug products that present demonstrable difficulties for compounding (Difficult to Compound List).

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

### **A. Glycolic Acid (Tab 1)**

1. Nominations (**Tab 1a**)
  - (a) Fagron
  - (b) National Community Pharmacists Association
  - (c) International Academy of Compounding Pharmacists
2. FDA Review (**Tab 1b**)

### **B. Trichloroacetic Acid (Tab 2)**

1. Nominations (**Tab 2a**)
  - (a) Fagron
  - (b) International Academy of Compounding Pharmacists
  - (c) Professional Compounding Centers of America
  - (d) National Community Pharmacists Association
2. FDA Review (**Tab 2b**)

### **C. Kojic Acid (Tab 3)**

1. Nominations (**Tab 3a**)
  - (a) Fagron
  - (b) National Community Pharmacists Association
  - (c) International Academy of Compounding Pharmacists
2. FDA Review (**Tab 3b**)

#### **D. Diindolylmethane (Tab 4)**

1. Nominations (**Tab 4a**)
  - (a) Fagron
  - (b) International Academy of Compounding Pharmacists
2. FDA Review (**Tab 4b**)

#### **E. Vasoactive Intestinal Peptide (Tab 5)**

1. Nomination (**Tab 5a**)
  - (a) Hopkinton Drug
2. FDA Review (**Tab 5b**)

### **III. Drug Products and Categories of Drug Products That Present Demonstrable Difficulties for Compounding**

#### **A. Proposed Evaluation Criteria**

The proposed criteria for evaluating whether a drug product or category of drug products presents demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act are found within the document attached at **Tab 6**.

#### **B. Drug Products That Employ Transdermal or Topical Delivery Systems (Tab 7)**

1. Nomination (**Tab 7a**)
  - (a) Public Citizen
2. FDA Review (**Tab 7b**)

## **IV. Draft Points to Consider**

### **A. November 3, 2016, a.m. session**

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

1. FDA is proposing that glycolic acid, up to 70%, for topical use be INCLUDED on the 503A Bulks List. Should glycolic acid be placed on the list?
2. FDA is proposing that trichloroacetic acid for topical use be INCLUDED on the 503A Bulks List. Should trichloroacetic acid be placed on the list?
3. FDA is proposing that kojic acid NOT be included on the 503A Bulks List. Should kojic acid be placed on the list?

### **B. November 3, 2016, p.m. session**

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

1. FDA is proposing that diindolylmethane NOT be included on the 503A Bulks List. Should diindolylmethane be placed on the list?
2. FDA is proposing that vasoactive intestinal peptide NOT be included on the 503A Bulks List. Should vasoactive intestinal peptide be placed on the list?

#### **Draft Points for the PCAC to Consider Regarding Whether to Include Certain Drug Products or Categories of Drug Products on the Difficult to Compound List**

3. FDA is proposing that drug products that employ transdermal or topical delivery systems be INCLUDED on the Difficult to Compound List under sections 503A and 503B of the FD&C Act. Should drug products that employ transdermal or topical delivery systems be placed on the list?

Tab 1

Glycolic Acid

Tab 1a

# Glycolic Acid Nominations

# Fagron

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



<b>What is the name of the nominated ingredient?</b>	<b>Glycolic Acid</b>
<b>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</b>	
<b>Is the ingredient listed in any of the three sections of the Orange Book?</b>	The nominated substance was searched for in all three sections of the Orange Book located at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm</a> . The nominated substance does not appear in any section searches of the Orange Book.
<b>Were any monographs for the ingredient found in the USP or NF monographs?</b>	The nominated substance was searched for at <a href="http://www.uspnf.com">http://www.uspnf.com</a> . The nominated substance is not the subject of a USP or NF monograph.
<b>What is the chemical name of the substance?</b>	2-hydroxyethanoic acid
<b>What is the common name of the substance?</b>	Hydroxyacetic acid; Ácido hidroxiacético ;Glicólico, ácido; Hydroxyacetic Acid
<b>Does the substance have a UNII Code?</b>	0WT12SX38S
<b>What is the chemical grade of the substance?</b>	No grade

<b>What is the strength, quality, stability, and purity of the ingredient?</b>	Description: White, crystalline powder Identification: Conforms Melting Range Start: $\geq 72^{\circ}\text{C}$ Melting Range Finish: $\leq 80^{\circ}\text{C}$ Chloride: $\leq 20$ ppm Sulfate: $\leq 500$ ppm Iron: $\leq 10$ ppm Heavy Metals: $\leq 10$ ppm Assay (HPLC): $\geq 99.0\%$
<b>How is the ingredient supplied?</b>	Powder, Liquid
<b>Is the substance recognized in foreign pharmacopeias or registered in other countries?</b>	No
<b>Has information been submitted about the substance to the USP for consideration of monograph development?</b>	No
<b>What dosage form(s) will be compounded using the bulk drug substance?</b>	Lotion, gel
<b>What strength(s) will be compounded from the nominated substance?</b>	1-70%
<b>What are the anticipated route(s) of administration of the compounded drug product(s)?</b>	Topical
<b>Are there safety and efficacy data on compounded drugs using the nominated substance?</b>	Ditre, Cherie M. "Glycolic acid peels." <i>Dermatologic Therapy</i> 13.2 (2000): 165-172. <a href="http://onlinelibrary.wiley.com/doi/10.1046/j.1529-8019.2000.00024.x/full">http://onlinelibrary.wiley.com/doi/10.1046/j.1529-8019.2000.00024.x/full</a>  Coleman 3rd, W. P., and J. M. Futrell. "The glycolic acid trichloroacetic acid peel." <i>The Journal of dermatologic surgery and oncology</i> 20.1 (1994): 76-80. <a href="http://europepmc.org/abstract/MED/8288810">http://europepmc.org/abstract/MED/8288810</a>  Sarkar, Rashmi, et al. "The Combination of Glycolic Acid Peels With a Topical Regimen in the Treatment of Melasma in Dark-Skinned Patients: A Comparative Study." <i>Dermatologic surgery</i> 28.9 (2002): 828-832. <a href="http://onlinelibrary.wiley.com/doi/10.1046/j.1524-4725.2002.02034.x/full">http://onlinelibrary.wiley.com/doi/10.1046/j.1524-4725.2002.02034.x/full</a>  Burns, Robert L., et al. "Glycolic acid peels for postinflammatory hyperpigmentation in black patients." <i>Dermatologic surgery</i> 23.3 (1997): 171-175. <a href="http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4725.1997.tb00014.x/abstract">http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4725.1997.tb00014.x/abstract</a>

<p><b>Has the bulk drug substance been used previously to compound drug product(s)?</b></p>	<p>Yes, as a chemical peel (15%) and a lotion (5).</p> <p>Chemical Peel: 30 days per USP &lt;795&gt;</p> <p>Allen, Loyd. "Glycolic Acid 15% Gel." International Journal of Pharmaceutical Compounding. 6.2 (2002):128.</p> <p>Lotion: Hydrocortisone 1%, Hydroquinone 5% and Glycolic Acid 5% Lotion 30 days per USP &lt;795&gt;</p> <p>Allen, Loyd. "Basics of Compounding for Skin Discolorations." International Journal of Pharmaceutical Compounding. 8.5(2004):376-380.</p>
<p><b>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</b></p>	<p>It has been used in topical preparations for hyperpigmentation and photodamaged skin</p>
<p><b>What is the reason for use of a compounded drug product rather than an FDA-approved product?</b></p>	<p>No FDA approved Glycolic Acid preparation. Glycolic acid is used for pigmentation disorders of the skin. Hyperpigmentation is a concern for many individuals. The FDA approved preparation Tri Luma (Fluocinolone, Hydroquinone, and tretinoin) is available for hyperpigmentation. It has had frequent supply interruptions and side effects include rash, blisters, skin bumps, tiny red lines or blood vessels showing, and gradual blue black darkening of skin. Glycolic acid is found to have effects alone but much better in combination with FDA approved ingredients such as Hydroquinone for hyperpigmentation disorders. Advantages are to create synergy and allow for lower dosing of other ingredients which can lead to decreased side effect profiles.</p>
<p><b>Is there any other relevant information?</b></p>	

National Community Pharmacists Association -- Glycolic Acid -- 503A Nomination

<b>Ingredient Name</b>	Glycolic acid
<b>Chemical Name</b>	2-hydroxyacetic acid; hydroxyethanoic acid
<b>Common Name</b>	Glycolic acid
<b>UNII Code</b>	0WT12SX38S
<b>Description of strength, quality, stability and purity</b>	From PCCA MSDS: 70% by weight and stable; avoid to oxidizing agents.
<b>Ingredient Format(s)</b>	Crystal, Granula, 70% Solution
<b>Recognition in Pharmacopeias</b>	Not USP; sold OTC in US as a dietary supplement.
<b>Final Compounded Formulation Dosage Form(s)</b>	Foaming gel; Solution; Serum; Topical Peel; Gel; Cleanser; Cream; Paste; Lotion; Shampoo; Ointment
<b>Final Compounded Formulation Strength</b>	0.08%; 0.5%; 1% ; 1.3% ; 1.5%; 1.75%; 2%; 2.5%; 3.5%; 4%; 5%; 5.5%; 5.6%; 7.5% ; 8%; 10%; 15%; 20%; 25%; 30%; 50%; 70%
<b>Final Compounded Formulation Route(s) of Administration</b>	Topical      Subcutaneous Injection
<b>Bibliographies on Safety and Efficacy Data</b>	
<b>Final Compounded Formulation Clinical Rationale and History of Past Use</b>	Above 20% it is used for anesthetic. Below 20% used for cosmetics. Keratosis, wart exfoliate



## **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**

<b>Ingredient Name</b>	Glycolic Acid
<b>Chemical/Common Name</b>	Hydroxyacetic Acid; Hydroxyethanoic Acid
<b>Identifying Codes</b>	79-14-1
<b>Chemical Grade</b>	Provided by FDA Registered Supplier/COA
<b>Description of Strength, Quality, Stability, and Purity</b>	Provided by FDA Registered Supplier/COA
<b>How Supplied</b>	Varies based upon compounding requirement
<b>Recognition in Formularies</b> <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

### **Information on Compounded Bulk Drug Preparation**

<b>Dosage Form</b>	Varies based upon compounding requirement/prescription
<b>Strength</b>	Varies based upon compounding requirement/prescription
<b>Route of Administration</b>	Varies based upon compounding requirement/prescription
<b>Bibliography</b> <i>(where available)</i>	

**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.



## **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**

<b>Ingredient Name</b>	Glycolic Acid, 70%
<b>Chemical/Common Name</b>	Glycolic Acid, 70%
<b>Identifying Codes</b>	79-14-1
<b>Chemical Grade</b>	Provided by FDA Registered Supplier/COA
<b>Description of Strength, Quality, Stability, and Purity</b>	Provided by FDA Registered Supplier/COA
<b>How Supplied</b>	Varies based upon compounding requirement
<b>Recognition in Formularies</b> <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

### **Information on Compounded Bulk Drug Preparation**

<b>Dosage Form</b>	Varies based upon compounding requirement/prescription
<b>Strength</b>	Varies based upon compounding requirement/prescription
<b>Route of Administration</b>	Varies based upon compounding requirement/prescription
<b>Bibliography</b> <i>(where available)</i>	

**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.

Tab 1b

# FDA Review of Glycolic Acid



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 29, 2016

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Glycolic Acid for Inclusion on the 503A Bulk Drug Substances List

## I. INTRODUCTION

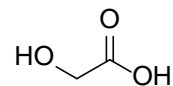
Glycolic acid, 0.08% to 70%, has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of hyperpigmentation and photodamaged skin. It was also nominated for subcutaneous injection and topical use as an anesthetic and in the treatment of keratosis and warts. This review will focus only on topical use in hyperpigmented and photodamaged skin because adequate support was not provided for the other nominated uses.

We have reviewed 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 in favor* of placing glycolic acid, 0.08% to 70%, for topical use 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).<sup>1</sup>

## II. EVALUATION CRITERIA

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

Glycolic acid, also known as hydroxyacetic acid, is a small organic molecule with the following molecular structure:



This substance is currently marketed in cosmetics in various dosage forms, including creams, pads, and lotions.

Databases searched for information on glycolic acid in regard to Section II.A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and US Pharmacopoeia/National Formulary.

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<sup>1</sup> 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 (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 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)).

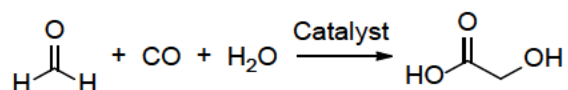
### 1. *Stability of the API and likely dosage forms*

No stability issues have been reported for glycolic acid in the literature. It is very likely to be stable either as a solid or in aqueous solutions, especially at low pH values, since glycolic acid is usually self-preserving (Villiers et al., 1997). Therefore, this compound is very likely to be stable under ordinary storage conditions in the proposed dosage forms, such as lotions and gels.

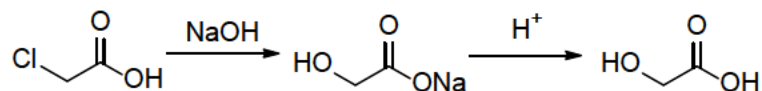
### 2. *Probable routes of API synthesis*

There have been various synthetic routes to prepare glycolic acid. The two methods most commonly used are shown below.

Route 1: Industrial synthesis of glycolic acid in the United States is based on the reaction between formaldehyde with carbon monoxide and water in the presence of catalyst at > 30 MPa (John 1939).



Route 2: Glycolic acid is also produced in large quantities by treating monochloroacetic acid with sodium hydroxide (or other bases) followed by acidification (Witzemann 1917; Ebmeyer et al., 1998). This method usually results in products with higher purity compared with route 1, described above.



### 3. *Likely impurities*

Likely impurities may include:

- Residual starting materials, such as formaldehyde in route 1 and monochloroacetic acid in route 2
- Residual catalysts or reagents used in the reaction
- Side products, byproducts or reaction intermediate from the reaction, such as sodium chloride in route 2 or formic acid and methoxyacetic acid in route 1

### 4. *Toxicity of those likely impurities*

Formaldehyde and formic acid from synthetic route 1 and monochloroacetic acid from route 2 can have toxicities depending on the exposure level. Further toxicity issues are discussed in section B.

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

Glycolic acid is a colorless crystalline solid that is highly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability was 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*

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

**Conclusions:** Glycolic acid is a well-characterized small molecule, and it is likely to be stable under ordinary storage conditions. It is easily characterized with various analytical techniques, and the preparation of glycolic acid has been well developed. Based on the available information, there are no concerns about the physical and chemical characterization of glycolic acid as a bulk drug substance that can be used for compounding under section 503A of the FD&C Act, when potential impurities in the drug substance, such as formaldehyde, are controlled at acceptable levels.

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

1. *Nonclinical Assessment*

The following public database(s) were consulted in the preparation of this review: PubMed, TOXNET, and Google/Google Scholar.

a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

Glycolic acid, an alpha-hydroxyl acid (AHA), has been widely used in cosmetic and skin care products. In low concentrations (4 to 10%), it has been used to ameliorate the appearance of skin aging. In higher concentrations (> 20%), it has been used as a chemical peel in conditions such as calluses, keratoses, acne, psoriasis, and photoaging (Kornhauser et al., 2010). Glycolic acid is believed to facilitate progressive weakening of cohesion of the intercellular material of the stratum corneum, resulting in uniform exfoliation of its outermost layers (the stratum disjunctum). A study in human volunteers with a 4% glycolic acid formulation indicated that the mechanism of action of glycolic acid on the stratum corneum appears to be a targeted desmosomal action (restricted to the stratum disjunctum) without disrupting the barrier structures of the stratum corneum (Fartasch et al., 1997).

Wang (1999) proposed the following theory for the mechanism of action of AHAs: AHAs reduce the calcium ion concentration in the epidermis and remove calcium ions from the cell adhesions by chelation. This causes a loss of calcium ions from the cadherins of the desmosomes and adherens junctions, from the tight junctions, and possibly also from other divalent metallic cation-dependent cell adhesion molecules. The cell adhesions are thereby disrupted, resulting in desquamation.

In a study using human skin biopsy specimens, epidermal and dermal hyaluronic acid content and collagen gene expression were all increased in glycolic acid-treated skin as compared to vehicle-treated controls (Bernstein et al., 2001). Another study conducted by Olkano et al. (2003) showed that glycolic acid not only directly accelerated collagen synthesis by fibroblasts, but that it also modulated matrix degradation and collagen synthesis through keratinocyte-

released cytokines. Usuki et al. (2003) showed that glycolic acid directly suppressed melanin formation in melanocytes by inhibiting tyrosinase activity.

#### b. Safety pharmacology

The effect of 0.35 to 0.8 mmol/kg glycolic acid on cyclopropane/epinephrine-induced cardiac arrhythmias was examined in dogs (White and Stutzman, 1950). Intravenous doses of 0.35 to 0.5 mmol/kg glycolic acid increased the duration of arrhythmias whereas doses > 0.5 mmol/kg decreased or totally eliminated the arrhythmias. Central nervous system depression was observed at higher doses. Glycolic acid, 1000 mg/kg given intraperitoneally, was a potent inhibitor of oxygen consumption and glucose metabolism in rat liver and myocardium in vivo, but it did not have an effect on brain oxygen consumption (Lamothe et al., 1971).

#### c. Acute toxicity

The oral LD<sub>50</sub> of glycolic acid was 1950 and 1920 mg/kg in rats and guinea pigs, respectively (Smyth et al., 1941). The oral LD<sub>50</sub> of glycolic acid was 2000 mg/kg in mice (Perier et al., 1988). The inhalation LC<sub>50</sub> of glycolic acid in rats was 7.1 mg/L/4h (Kennedy and Burgess, 1997).

Single topical doses of 50% and 70% glycolic acid were applied to a 2 cm x 2 cm area of the back of two minipigs for 15 min (Moy et al., 1996). Epidermal and dermal necrosis was induced by 70% glycolic acid after 1 day. Some inflammatory infiltrate and dermal growth were observed with 50% and 70% glycolic acid after 7 and 21 days, respectively.

Glycolic acid in high concentrations (70% technical grade solution and pure) causes local effects that are typical of a strong acid, such as dermal and eye irritation. Skin contact may cause severe skin irritation with discomfort or rash. Prolonged exposure may cause skin burns or ulceration. Eye contact may cause eye corrosion with corneal or conjunctival ulceration. Permanent eye damage, even blindness, can occur (Material Safety Data Sheet (MSDS) from ScienceLab.com, 2013).

In a modified Draize test (species and number of animals not stated) in which 3% glycolic acid was used for the intradermal injection challenge and 60% glycolic acid was used for the topical application challenge, glycolic acid was not shown to be a sensitizer (Cosmetic Ingredient Review Expert Panel (CIREP), 1998).

#### d. Repeat dose toxicity

Topical doses of 3 mg/cm<sup>2</sup> of 0 (control: Vaseline), 5% or 10% glycolic acid (pH 3.0) were administered to two prewashed 5 cm x 8 cm areas on the back of hairless guinea pigs once daily for 3 weeks. Some erythema and/or flaking of the skin were noted in the two dose groups. At microscopic examination, treated skin had a thickening of the epidermis after treatment with 5% or 10% glycolic acid. Up to a 4-fold increase in viable epidermal thickness was observed for the glycolic acid-treated skin as compared to the Vaseline-treated or untreated skin. Although these

epidermal changes were observed in glycolic acid-treated skin, the barrier integrity of glycolic acid- and control-treated skin was not significantly different (CIREF 1998).

Groups of 10 male Wistar rats were fed a basal diet or the basal diet with 3% glycolic acid for 4 weeks to examine the effects of glycolic acid on calculi formation (Chow et al., 1978). The addition of glycolic acid to a basal diet resulted in decreased body weight gain and increased water intake. Glycolic acid was a potent calculi inducer, with deposits being observed in the ureters, urinary bladder, renal tubules, and/or renal pelvis, and papilla of all 10 rats.

Oral doses of 97 and 194 mg/kg/day glycolic acid were given to cats for 7 to 48 and 28 to 59 days, respectively (Krop and Gold 1944). In the low-dose group, signs of toxicity appeared after 7 to 20 days of dosing; urinary and blood changes were observed, and 4 of the 6 animals had weight loss (7% to 24%). In the high-dose group, signs of toxicity appeared after 4 to 17 days of dosing and weight loss ranged from 9% to 30%. One of 6 animals of the low-dose group and all 8 animals of the high-dose group died during the study.

Dogs (number and sex not specified) were given daily oral doses of 1000 mg glycolic acid for 35 days. No abnormal secretions of oxalic acid were found, and no damage to the gastrointestinal tract or kidneys was reported (CIREF 1998).

Groups of male rats were exposed by inhalation to 0 (control), 0.16, 0.51, or 1.4 mg/L glycolic acid, 6 hours/day, 5 days/week for 2 weeks (Kennedy and Burgess, 1997). The high dose was not well tolerated, with treatment being discontinued after 8 exposures, and 7 rats were terminated following labored breathing, lung noise, nasal and ocular discharge, and severe weight loss. Clinical pathology changes included decreases in serum protein, increases in both ALT and ALP, and decreases in urine volume and pH. These changes were reversible in the 3 surviving rats after a 10-day recovery period without treatment. Histopathological changes in this group included diffuse hepatocellular degeneration and thymus atrophy. One rat administered mid-dose died after 10 exposures. In animals exposed to mid-dose, clinical and microscopic pathology indicated liver and thymus damage, with clinical pathology changes being reversible. The tissues of the upper respiratory tract appeared normal at sacrifice but were not examined microscopically. The only effect seen at low dose was a very mild, diffuse hepatocellular degeneration seen in one of 10 rats examined 14 days post-exposure.

Oral (gavage) doses of 0, 150, 300 and 600 mg/kg/day glycolic acid (diluted in water) were administered to SD rats (40/sex/group). Ten animals/sex/group were designated for the evaluation of subchronic toxicity, immunotoxicity, neurotoxicity, or reproductive toxicity. In the subchronic toxicity and neurotoxicity studies, animals were treated for 13 weeks. The immunotoxicity assessment was performed by injecting sheep red blood cells (SRBC) in the tail vein of the assigned animals on day 23 and euthanizing the animals on day 29. For the evaluation of subchronic toxicity, outcomes assessed included: survival, body weight, food consumption, food efficiency, ophthalmic examination, clinical signs, organ weights, hematology, urinalysis, clinical chemistry, and histopathology. For the evaluation of neurotoxicity, outcomes assessed included a functional observational battery (FOB) and motor activity evaluations. Complete histopathological examination was performed for the control and high-dose groups; only liver, kidney, lung, and gross lesions were examined for the mid-dose

group; and no tissues were examined for the low-dose group. Two compound-related deaths occurred at high dose. Decrease in mean body weight, overall body weight gain, food consumption, and food efficiency occurred in males and females at mid-dose and high-dose. These effects were considered adverse in the high-dose group only (no further details provided). Toxicologically significant increases in blood neutrophils, urea nitrogen, phosphorous, and creatinine, and decreases in urine concentration were noted at mid dose and high dose. Mean absolute and relative kidney weights increased in male rats administered the mid dose or high dose. Gross findings of renal pelvis dilation, microscopic findings of oxalate crystal nephrosis and unilateral hydronephrosis, and hyperplasia of the transitional epithelium of the renal pelvis (considered secondary to irritation) were also observed (in males only) at these dose levels. No organ weight, gross or microscopic findings indicative of systemic toxicity were observed in female rats administered mid-dose or high-dose. Finally, microscopic findings (not specified) were observed in the respiratory tract (upper airways and lungs) of all treated animals and were thought to be a result of irritation from aspiration of glycolic acid following exposure via gavage. The immune response of the treated animals was not apparently affected by the treatment. The neurotoxicity study did not reveal any treatment-related neurobehavioral or neuropathological effects. The no-observed-adverse-effect level (NOAEL) for subchronic toxicity was identified as 150 mg/kg/day in this study. The NOAEL for immunotoxicity or neurotoxicity was identified as 600 mg/kg/day, the highest dose tested in this study (Non-human toxicity experts for glycolic acid/HSDB/TOXNET and CalEPA, 2001). For reproductive toxicity findings, see section II.B.1.f.

Albino rats were fed 0.5%, 1%, and 2% glycolic acid for ~200 to 250 days in a 1943 General Foods Corporation study. Decreased growth weight, an increase in renal oxalate, and nephrotoxic effects were observed in male rats fed 1% or 2% glycolic acid. No effects were observed in female rats or in male rats fed 0.5% glycolic acid. Mortality was 60% and 70% for the 1% and 2% dose groups, respectively, with deaths beginning at day 89 (CIREP 1998).

#### e. Mutagenicity

An Ames test was conducted with 20% glycolic acid, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation. Doses of 10 to 5000 µg/plate were tested in the main assay. The pH of the test article was 4.0. No positive responses were observed with or without metabolic activation in any of the test strains, and no precipitate or appreciable toxicity was observed. Glycolic acid was not mutagenic in this Ames test (CIREP 1998).

Another Ames test was conducted with 70% glycolic acid, using *S. typhimurium* strains TA97a, TA98, TA100, TA1535, and *E. coli* strain WP2 *uvrA*, with and without metabolic activation. Doses of 1 to 5000 µg/plate were tested in this study. Glycolic acid was negative for mutagenicity in this Ames test (CalEPA 2001).

A mouse lymphoma assay was conducted with 70% glycolic acid, using L5178Y TK<sup>+/−</sup> Mouse Lymphoma cell line, with and without metabolic activation. Doses of 39.3 to 5000 µg/mL were tested in the initial assay and doses of 250 to 5000 µg/mL were tested in the confirmatory assay. An increase in mutant frequency (> 2-fold of the control value) was evident for the activated

samples at doses > 2500 mg/mL. However, because the dose level was in excess of the treatment concentration limit of 10 mM, such increase is not considered to be a positive response (CalEPA 2001).

A chromosome aberration assay using CHO-K1 cells was conducted with 20% glycolic acid, with and without metabolic activation. The doses tested in the main assay were 625 to 5000 µg/mL. Test article pH was adjusted to ~ 6.5. At the highest dose, 5000 µg/mL, toxicity (mitotic inhibition) was approximately 10% and 43% with and without metabolic activation, respectively. The percentage of cells with structural aberrations in the test groups, both with and without metabolic activation, were not significantly increased as compared to the solvent control. Glycolic acid was negative for clastogenicity in this assay (CIREP 1998).

In a mouse bone marrow micronucleus assay, 5 CD-1 mice/sex/time point were dosed orally by gavage with 0, 1200 (males), or 1600 (females) mg/kg glycolic acid (70% solution) and euthanized at 24 and 48 hours after dosing. In addition, 5 mice/dose were dosed with 300 or 600 (males) mg/kg, or 400 or 800 (females) mg/kg glycolic acid and euthanized at 24 hours after dosing. To ensure that 5 animals/sex/dose were available for analysis, 5 additional males were dosed with 1200 mg/kg and 3 additional females with 1600 mg/kg glycolic acid because 5 males administered high doses and 3 females administered high doses died over the course of the study. Clinical signs included lethargy, moribundity, and abnormal gait. Bone marrow samples from the femur were examined and the percentage of polychromatic erythrocytes (PCE) with a micronucleus and the ratio of PCE to normochromatic erythrocytes were determined. No treatment-related increase in the number of micronucleated PCEs was noted. Glycolic acid was negative for clastogenicity in this assay (CalEPA 2001).

f. Developmental and reproductive toxicity

Oral (gavage) doses of 0, 150, 300 and 600 mg/kg/day glycolic acid (diluted in water) were administered to SD rats (10/sex/group) for 13 weeks. Animals were allowed to mate within their treatment group starting on day 97. It is not clear if the animals were exposed to glycolic acid during the reproductive portion of the study. There were significant decreases in body weights among parental females in the mid-dose and high-dose groups during gestation and in the females administered high-dose on day zero of lactation. The only parameter in which statistical significance was demonstrated was the smaller litter size of the high-dose group. However, the mean value was within the historical control range and thus was considered to be of minimal consequence. The NOAEL for reproductive and developmental toxicity was 600 mg/kg/day under the study conditions (Non-human toxicity experts for glycolic acid/HSDB/TOXNET and CalEPA 2001).

In a pilot developmental toxicity study in female CrI:CD BR rats, oral gavage doses of 0, 125, 250, 500, and 1000 mg/kg/day glycolic acid were administered to rats (8/group) on gestation days 7 to 21. Surviving dams were sacrificed on day 22 and the fetuses were examined. Maternal toxicity was observed at doses of 500 and 1000 mg/kg/day. Wet chin and lung noise were noted in females of the 500 mg/kg/day group. Abnormal gait and mobility, lung noise, salivation, and stained and wet haircoats were observed for dams given high dose. Maternal body weights for animals of this dose group were significantly reduced (88% of control) on day

22. One moribund high-dose female was terminated early. Ulcerations of the gastric mucosa, distended intestine, and mottled kidneys were observed at necropsy. Fetuses of the 500 mg/kg/day group had significantly decreased mean fetal weight, and the incidence of retarded sternebral ossification was increased. Fetuses of the 1000 mg/kg/day group had significantly decreased mean fetal body weight, and the incidence of early resorptions, specific malformations [gastroschisis, hydrocephaly, fused ribs, fused vertebra(e), and hemivertebra(e)], and specific variations [misaligned sternebra(e) and retarded vertebral and sternebral ossification] were significantly increased. The maternal and developmental NOAEL was 250 mg/kg/day in this study (CIREP 1998).

Oral (gavage) doses of 0, 75, 150, 300, and 600 mg/kg/day glycolic acid were administered to female Crl:CD BR rats (25/group) during gestation days 7 to 21. The dams were euthanized on day 22, and the fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations. Clear evidence of maternal toxicity was demonstrated at 600 mg/kg/day (wheezing/lung noise, abnormal gait/staggering, lethargy). In addition, maternal body weights, weight changes, and food consumption were significantly reduced at this dose level. Marginal evidence of maternal toxicity was demonstrated at 300 mg/kg/day (wheezing/lung noise observed in two of 25 dams). There was marked evidence of developmental toxicity at 600 mg/kg/day. Mean fetal weight was significantly reduced while the incidences of skeletal (ribs, vertebra, and sternebra) malformations and variations were significantly increased. At 300 mg/kg/day, there was a slight (two affected fetuses from two litters) increase in the incidence of two skeletal malformations: fused ribs and fused vertebrae. Although these increases were not statistically significant, they were consistent with findings seen at 600 mg/kg/day and thus were considered relevant. There was no other evidence of developmental toxicity at 300 mg/kg/day nor was any developmental toxicity seen at 150 or 75 mg/kg/day. Thus, the maternal and developmental NOAEL was considered to be 150 mg/kg/day (Munley et al., 1999).

#### g. Carcinogenicity

Male and female Crl:SKH-1 hairless mice were topically exposed to glycolic acid (0%, 4%, or 10% cream, pH 3.5, applied at 2 mg/cm<sup>2</sup>) with simulated solar light (SSL) radiation [0, 0.3, 0.6, or 0.9 minimal erythema dose (MED)] using a filtered 6.5 kW xenon arc light source for 40 weeks, and the mice were held an additional 12 weeks after the treatment. The addition of glycolic acid (4% or 10%) did not affect the time to tumor formation in male or female mice at either SSL dose when compared to mice receiving the control cream. Glycolic acid did not affect the photocarcinogenesis of simulated solar light in this study (National Toxicology Program (NTP) 2007).

Hong et al., (2001) also conducted a photocarcinogenicity study in SKH-1 hairless mice with glycolic acid. Female hairless mice (15/group) were irradiated for 5 days per week at a total dose of 74.85 J/cm<sup>2</sup> UVA and 2.44 J/cm<sup>2</sup> UVB for 22 weeks. Glycolic acid [30 mg in a cream base made with PEG 400 and 8000 (1:2), pH 3.0] combination was applied topically twice a week at a dose of 8 mg/cm<sup>2</sup> immediately after UV irradiation. In this study, glycolic acid reduced UV-induced skin tumor development. The protective effect of glycolic acid was a 20% reduction of skin tumor incidence, a 55% reduction of tumor multiplicity (average number of tumors/mouse), and a 47% decrease in the number of large tumors (larger than 2 mm). Glycolic

acid also delayed the first appearance of tumor formation by about 3 weeks. It should be noted that there were many differences between this study and the NTP study described above, which may account for the result difference. The light source was different (UV vs. SSL); the test formulation was different; the topical dose of glycolic acid was different; and there was no vehicle control group in the study conducted by Hong et al.

#### h. Toxicokinetics

No information found.

**Conclusions:** Glycolic acid in high concentrations is used as a chemical peel as it causes exfoliation of stratum disjunctum and epidermal remodeling. Glycolic acid in very high concentrations causes local effects that are typical of a strong acid, such as dermal and eye irritation. It also induces significant toxicity via inhalation (target organs: lung, liver, and thymus). However, its acute oral toxicity is considered low (LD<sub>50</sub> ~2000 mg/kg). Repeat dose oral toxicity studies in rats showed that glycolic acid induced calculi formation (target organs: urinary bladder and kidney) after 4 weeks of dosing while such finding was not seen in dogs after 35 days of oral dosing of 1000 mg/kg/day glycolic acid. In a 13-week oral toxicity study in rats, renal toxicity was noted at 300 and 600 mg/kg/day (NOAEL identified as 150 mg/kg/day) while immunotoxicity or neurotoxicity was not seen at doses up to 600 mg/kg/day, the highest dose tested.

Glycolic acid was not mutagenic or clastogenic in various genotoxicity assays. It is not a skin sensitizer in nonclinical studies. It has not demonstrated photocarcinogenic potential. In oral reproductive and developmental toxicity studies in rats, it induced developmental toxicity at high maternal toxic doses. In a pivotal study in rats, the NOAEL for developmental toxicity was identified as 150 mg/kg/day. There is lack of nonclinical data for the evaluation of chronic dermal toxicity and dermal carcinogenic potential of glycolic acid.

Overall the nonclinical data of glycolic acid do not raise serious safety concerns when it is used topically at low concentrations.

## 2. *Human Safety*

The following databases were consulted in the preparation of this review: PubMed, the Cochrane Library, and EMBASE.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for glycolic acid through December 14, 2015, and retrieved 45 cases.

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 associated with glycolic acid on December 30, 2015, and retrieved 19 cases.

Glycolic acid's topical application enhances photoirritation by ultraviolet light. Because of the potential to enhance sensitivity to sunburn, a CFSAN guidance for industry<sup>2</sup> recommends that labeling for cosmetics containing AHAs intended for topical application to the skin or mucous membranes include the following statement:

*Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.*

a. Reported adverse reactions (FAERS, CAERS, Clinical Trials and Case Reports)

Of the 45 cases retrieved from the FAERS search, none specified the use of a compounded product. Of the 43 cases that could be evaluated, 38 reported the use of commercial products and 5 did not specify the glycolic acid product used. Patient age, reported in 40 cases, ranged from 16 to 70 years. Acne was the most frequently reported indication for use, reported in 33 cases. Thirty-nine reported serious outcomes,<sup>3</sup> and no deaths were reported. However, the majority of cases are confounded due to the presence of ingredients like benzoyl peroxide, salicylic acid, witch hazel, and/or others in the products used, or concomitant use of other topical products.

Thirty-two of the cases reported adverse events associated with the use of Proactiv or Proactiv Plus over-the-counter (OTC) multi-product acne treatment regimens. The cases primarily reported application site reactions, events suggestive of hypersensitivity reactions, or both. The application site reactions included erythema, dryness, peeling, burns, swelling, tingling, pruritus, pain, and contact dermatitis. Symptoms suggestive of hypersensitivity reactions included generalized itching, generalized hives or rash, tongue swelling, throat tightness, inability to swallow, and difficulty breathing. Other events included seizures in a patient with a seizure history, and photopsia in a patient evaluated by an ophthalmologist and general practitioner, with no cause identified. Each case reported the use of at least one product formulated with glycolic acid, but the majority of cases reported the use of five or more products, not all of which contained glycolic acid. The other active ingredients for the products included benzoyl peroxide, salicylic acid, sulfur, and hydroquinone.

One case, published in the medical literature, reported severe painful erythema, hyperpigmentation of the face and neck, and erosions in a 34-year-old female 3 days following a chemical peel with glycolic acid 70% (Gerber et al., 2014). Subsequently, she experienced post-inflammatory hyperpigmentation and scarring that persisted 2 months later. She had received glycolic acid peels at unspecified intervals for the past several months without problems. Her skin was prepared for the peel using 8% glycolic acid, and emollients and sunscreens were used

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<sup>2</sup> Guidance for industry: *Labeling for Cosmetics Containing Alpha Hydroxy Acids*, available online at [www.fda.gov/cosmetics/GuidanceRegulatory/GuidanceDocuments/ucm090816.htm](http://www.fda.gov/cosmetics/GuidanceRegulatory/GuidanceDocuments/ucm090816.htm).

<sup>3</sup> Serious outcomes are defined as death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

after the peel. At the initial referral, it was noted that for the preceding 10 weeks, she had taken self-prescribed isotretinoin 10 mg 3 times weekly for the treatment of coarse-pored skin. She had discontinued the isotretinoin for 3 weeks before at least one of the peels.

The following is a report of a systemic reaction to a product that contained multiple components, one of which was glycolic acid.

One case reported difficulty in breathing, swollen tongue, elevated blood pressure, erythema, and involuntary movement of the extremities and jaw 15 minutes following application of a chemical peel of “Alpha-Beta Solution” to the face of a 61-year-old female. The product was reported to include salicylic acid and a combination of AHAs, including glycolic acid. She had received injections of onabotulinumtoxinA six days previously for the treatment of migraines. Concurrent medications included alendronate, aspirin, oral and vaginal estradiol, and polyethylene glycol 3350. She was allergic to dogs and cats, and reported sensitivity to foods containing tyramine. One year previously, she had received the same chemical peel without adverse effects. She was treated with oral and intravenous diphenhydramine, and was discharged after being observed in the Emergency Room. Subsequently, she had allergy testing, which was negative for onabotulinumtoxinA, positive for the histamine control, and not reported for glycolic acid.

The following describes a systemic reaction reported to FDA to a product containing glycolic acid in conjunction with concomitant oral treatment with a monoamine oxidase inhibitor. The case reported palpitations, dizziness, tongue and generalized numbness, and difficulty in breathing within 15 minutes following the use of a commercial product reported as “Wrinkles,” containing an unspecified concentration of glycolic acid, in a 34-year-old female. Her blood pressure increased to 160/95 mm Hg (from a baseline of 104/72). Concurrent medications included phenelzine (Nardil), a monoamine oxidase inhibitor for 3 years for the treatment of depression, and esterified estrogens/methyltestosterone. She was allergic to mold and ragweed. She was treated with nitroglycerin and recovered in approximately 40 minutes. The reporting physician suspected a drug interaction between the phenelzine and glycolic acid.

Of the 19 cases retrieved by the CAERS search, 8 were associated with the use of Proactiv or Proactiv Plus OTC multi-product acne treatment regimens. The other 11 cases involved a variety of OTC topical products, not compounded products, containing glycolic acid. In 4 cases it was unclear whether glycolic acid was a component, and if so, at what strength. Reported application site reactions included burned skin, development of keloids, puffiness, swelling, dryness, white discoloration, peeling, intense redness, itchy eyes and facial scarring. Reported systemic complaints included palpitations, hives, throat closing, shortness of breath, panic attack and seizure.

The following paragraphs discuss some representative adverse events reported from the clinical trials of glycolic acid in the treatment of melasma, a type of hyperpigmentation.<sup>4</sup>

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<sup>4</sup> The majority of clinical studies of glycolic acid use in hyperpigmentation identified in the search are in patients with melasma.

Bari et al., (2002) reported “transient adverse reactions like burning, stinging and erythema” and noted that they were seen in most of the patients after the use of 40% to 60% glycolic acid and 20% to 30% salicylic acid (split-face study) following 2 weeks of “priming” both sides with 0.1% tretinoin cream.

Erbil et al., (2007) reported that “moderate to severe epidermolysis appeared in three patients with consequent mild post-inflammatory hyperpigmentation” after a combined treatment regimen including serial glycolic acid peels, topical azelaic acid cream, and adapalene gel in the treatment of 28 subjects with recalcitrant melasma. However, complete regression of these adverse effects was achieved in the 20-week treatment period.

Garg et al., (2008) reported: “All patients developed mild cutaneous erythema and superficial desquamation. Postpeel hyperpigmentation was seen in 20% of the patients receiving glycolic acid peels only while in patients using tretinoin and hydroquinone, 14.3% and 5.5% developed this side effect, respectively. In patients receiving glycolic acid peels only, milia developed in 26.6% of patients and nodulocystic acne in 5.5%. Persistent erythema was seen in a single patient who was put on hydroquinone. None of these side effects merited the stoppage of treatment.”

Park et al., (2011) in a comparison of 1064-nm Q-switched neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser alone vs laser plus 30% glycolic acid peels reported: “The main AEs were erythema, transient burning and slight edema of the face after treatment, which were generally mild and disappeared within 3 h. Superficial desquamation was treated with emollients, and no further intervention was required.”

Sarkar et al., (2002) in a comparison of triple combination cream (TCC- hydroquinone 5%, tretinoin 0.05%, hydrocortisone acetate 1%) alone vs TCC plus 30% to 40% glycolic acid peels, reported: “The patients in the peel group experienced focal erythema and mild burning during the peels. Two patients in the peel group developed focal superficial vesiculation which left behind post-inflammatory hyperpigmentation that subsided with the regular application of betamethasone dipropionate 0.05% cream twice a day... A persistent erythema was observed in two patients in the peel group and the patients were asked to use sunscreens and topical corticosteroids.”

A similar profile of adverse events was seen in the clinical trials in which glycolic acid was used on photodamaged skin.

Goldman et al., (2010) in a comparison of Vivite (a partially neutralized glycolic acid compound with natural antioxidants) vs Cetaphil moisturizing regimen, stated: “Four subjects in the Vivite group (15.4%) reported adverse events. Of these, the most common were erythema and dryness”.

Stiller et al., (1996) studied 67 subjects with photodamaged skin comparing 8% glycolic acid vs 8% L-lactic acid vs vehicle, and reported that “only erythema differed significantly between the  $\alpha$ -hydroxy acid creams and the vehicle. Overall, all 3 test

creams were well tolerated. Only 1 patient withdrew as a result of facial irritation owing to the 8% L-lactic acid cream. Twenty-two subjects (30%) experienced some degree of erythema at 1 or more treatment sites at 1 time. Significant increases in erythema with 8% L-lactic acid and 8% glycolic acid were observed on the forearms at week two. However, at no time did the average change in erythema for any treatment increase 1 full grade from baseline.”

b. Clinical trials assessing safety

We found no clinical trials that were specifically undertaken to assess safety. Safety assessments were among the study procedures in multiple clinical trials as noted in the examples above in section II.B.2.a.

c. Pharmacokinetic data

There are no reports of human pharmacokinetic studies following topical application of glycolic acid. Jiang and Qureshi (1998) reported percutaneous absorption results following in vitro topical application of glycolic acid to human skin using a flow-through diffusion cell system. Application of 4% glycolic acid formulated at pH 2.0 for 24 hours resulted in  $13.46 \pm 7.44\%$  and  $12.22 \pm 9.03\%$  of the applied dose recovered in the viable skin and the receptor fluid, respectively. When the product was formulated at pH 3.8, the amount absorbed significantly reduced to  $2.23 \pm 1.51\%$  and  $1.42 \pm 0.77\%$  in the viable skin and the receptor fluid, respectively. When solutions containing 4 to 60% glycolic acid at their native pH values between 2.0 and 0.67 were applied for 24 hours, the fraction of dose recovered in the receptor fluid increased with the increase in strength (and corresponding decrease in pH) with more than 80% of the dose penetrated into the receptor fluid for the 60% strength solution. The authors also reported that percutaneous absorption of glycolic acid is time-dependent, with greater fraction recovered in the receptor fluid following 24 hours of application compared to 6 hours of application. The data suggest that glycolic acid can be absorbed following topical application if formulated at its low native pH. The percutaneous absorption is reduced if formulated at higher pH such as pH 3.8 and duration of contact is shortened.

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

- Melasma

Fluocinolone acetonide, hydroquinone, and tretinoin Cream, 0.01%/4%/0.05% (Tri-Luma), is indicated for the short-term treatment of moderate-to-severe melasma of the face in the presence of measures for sun avoidance, including the use of sunscreens.

- Photoaging

There are numerous topical retinoids (e.g., tretinoin and tazarotene products) approved as “an adjunctive agent for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs.”

There are numerous injectable botulinum toxin type A products “indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.”

Botox Cosmetic is also “indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.”

Procedural (non-drug) therapies such as laser, microdermabrasion, and intense pulsed light are also available for the treatment of melasma and improving the manifestations of photodamaged skin.

### **Conclusions:**

The available data suggest that topical use of glycolic acid is mainly associated with local irritancy (e.g., burning, erythema, swelling, and less commonly, vesiculation), although serious outcomes have been reported with use of products containing glycolic acid as one of several or many ingredients, or concomitant use of other topical products. Reported adverse reactions generally appeared to be readily manageable and temporary in duration. However, some authors did report post-inflammatory hyperpigmentation and rarely, scarring. No information is available on long-term outcomes.

The reports of systemic reactions to products containing glycolic acid are also confounded by the presence of multiple other components in the products and/or the concomitant use of oral or topical agents.

The available information, including extensive clinical data accumulated since the 1990s, does not raise major safety concerns associated with the topical use of glycolic acid.

### **C. Are there concerns about whether a 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*

A literature search revealed 25 reports of studies involving the use of glycolic acid for the treatment of melasma and other forms of hyperpigmentation. There were no placebo controlled trials. There were 23 clinical trials, which included 14 active controlled trials: 10 involving the addition of glycolic acid peels to a regimen of topical therapy and 4 involving a comparison (split face design) of glycolic acid peels versus other products. There were an additional 3 trials involving combination products that included glycolic acid as a component and 2 open-label trials. Some of the above trials included endpoints traditionally associated with photoaging studies. In addition, there were 4 systematic reviews of treatment of melasma including a Cochrane review from 2010 that included glycolic acid in the list of products recommended for the treatment of melasma.

Two clinical trials specifically addressed manifestations of photoaging changes: one comparing glycolic acid to lactic acid and one comparing a combination crème containing glycolic acid and antioxidants

with an emollient. The following are some representative reports from the clinical trials of glycolic acid in the treatment of melasma and post-inflammatory hyperpigmentation.

Bari et al., (2002) reported a comparison of the use of 40% to 60% glycolic acid (right side of face) to 20% to 30% salicylic acid (left side of face) following 2 weeks of “priming” both sides of the face with 0.1% tretinoin cream in 40 subjects with mixed and epidermal type of melasma. In this 12-week trial, both regimens (glycolic acid and salicylic acid) resulted in a statistically significant improvement from baseline using the Melasma Area and Severity Index (MASI), percent change in lesional area, and photos as outcome measures. In group I (pre-treated with tretinoin), the mean MASI score at baseline was 13.30 (range 3.60 to 28.20), which was reduced to 5.72 (range 1.2 to 11.70) at 12 weeks ( $p < 0.001$ ). In group II (with no pre-treatment), the respective mean MASI scores were 12.41 and 6.44 ( $p < 0.001$ ). With regard to percent reduction in lesional area, in group I on the right half of the face (glycolic acid) the improvement was 45.7%, and on the left half (salicylic acid) it was 49.8% ( $p > 0.05$ ). In group II, the right half showed 37.1%, and the left half 43% improvement ( $p > 0.05$ ). There was no statistically significant difference between the peeling agents or the primed versus unprimed subjects.

Burns et al., (1997) reported a comparison of topical therapy with 2% hydroquinone/10% glycolic acid gel bid + 0.05% tretinoin cream qhs alone vs the same topical therapy plus 6 serial glycolic acid peels (50% to 68%) q 3 weeks in 19 African American women with post-inflammatory hyperpigmentation for a duration of 22 weeks. Evaluation was performed based on the Hyperpigmentation Area and Severity Index (HASI). The mean HASI score decreased by 50% (from 10.22 to 5.12) for the peel group and by 42% (from 8.70 to 5.00) for the control group at 22 weeks. The difference was not statistically significant.

Erbil et al., (2007) reported a prospective, randomized comparison of a combined treatment regimen including serial glycolic acid peels, topical azelaic acid cream and adapalene gel vs the topical azelaic acid cream and adapalene gel alone in the treatment of 28 subjects with recalcitrant epidermal melasma over a 20-week duration. In the chemical peel group, a percentage change of 83.08% in mean MASI scores was observed at week 20, compared with a 69.34% decrease in the control group ( $p = 0.001$  and  $p = 0.005$ , respectively; Wilcoxon signed ranks test). The results were statistically significant in favor of the peel group at weeks 12 ( $p = 0.013$ ), 16 ( $p = 0.035$ ) and 20 ( $p = 0.048$ ).

Garg et al., (2008) reported a prospective, single-blind comparison of 60 subjects with melasma (any type) randomly assigned to 3 groups for a duration of 6 months:

- Group I: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3
- Group II: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3 + 0.025% tretinoin
- Group III: glycolic acid peels (20 to 45%) q 2 weeks X 6 then q 4 weeks X 3 + 2% hydroquinone

Fifty subjects completed the trial, and all 3 groups had a statistically significant response with decreased MASI of 30%, 38% and 52% for groups I, II, and III, respectively. Thus, it was concluded that the hydroquinone was the most effective priming agent, followed by the tretinoin.

Hurley et al., (2002) reported a prospective, investigator-masked, split-face comparison of 21 subjects with epidermal or mixed melasma randomly assigned to glycolic acid peels (20% to 30%) q 2 weeks to

one side of the face while both sides of the face received 4% hydroquinone cream BID for 8 weeks. Physician Global evaluation showed that 8 patients had more improvement on the peeled side, and 7 were thought to have more improvement on the non-peeled side compared with baseline photographs. Two patients were thought to have no difference between the two sides. Both sides showed a statistically significant improvement from baseline, but there was not a statistically significant difference between the treatments.

Park et al., (2011) reported a randomized, observer-blinded, split-face comparison of 1062-nm Q-switched Nd:YAG laser alone vs laser plus 30% glycolic acid peels q 2 weeks X 3 in 16 Korean subjects with resistant, mixed-type melasma over 6 weeks. After treatment, significant improvements from baseline were seen in Mexameter and modified Melasma Area and Severity Index (mMASI) on both sides of the face. The combined therapy side achieved an average 32.6% improvement in Mexameter readings and 37.4% improvement in mMASI, compared with 22% and 16.7%, respectively, on the side treated with laser only ( $p \leq 0.05$ ).

The following describe some examples of clinical trials on glycolic acid in the treatment of manifestations of photodamaged skin.

Goldman et al., (2010) reported a randomized, investigator-masked comparison of Vivite Skin Care System (“partially neutralized glycolic compounds with natural antioxidants”) vs. Cetaphil cleanser and moisturizer in 36 subjects with photoaging in a 60 day trial. A similar proportion of subjects in each group had a 1-point improvement on the hyperpigmentation scale (42% of Vivite subjects, 44% of Cetaphil subjects). There were no statistically significant between-group differences in investigator rating of wrinkles. Subject assessments favored the Vivite group for improvement in wrinkling and texture change.

Stiller et al., (1996) reported a randomized, double-blind, vehicle-controlled comparison of 8% glycolic acid vs. 8% L-lactic Acid (LA) vs. vehicle cream in women with moderate to severe photodamaged skin over 22 weeks (74 enrolled; 67 completed). Outcome measures included a 9-point Investigator’s global assessment scale (IGA) and a similar 9-point scale for each of 7 clinical signs of photodamage (mottled hyperpigmentation, fine wrinkling, coarse wrinkling, laxity, sallowness, telangiectasia, and tactile roughness) as well as 3 signs and symptoms of irritation or intolerance to study medication (erythema, dryness, and scaling). The percentage of patients using either 8% glycolic acid or 8% LA creams on the face achieving at least 1 grade of improvement (on the IGA) in overall severity of photodamage was significantly greater than that using the vehicle cream (76% glycolic acid, 71% lactic acid, and 40% vehicle;  $p < 0.05$ ). On the forearms, treatment with glycolic acid was superior to the vehicle in improving the overall severity of photodamage and sallowness ( $p < 0.05$ ). LA was significantly superior to the vehicle in reducing the overall severity of photodamage ( $p < 0.05$ ), mottled hyperpigmentation ( $p < 0.05$ ), sallowness ( $p < 0.05$ ), and roughness on the forearms ( $p < 0.05$ ).

The table below displays results for the clinical trials described above and additional clinical trials for the use of glycolic acid in the treatment of melasma and other types of hyperpigmentation, as well as manifestations of photodamaged skin.

**Table 1: Clinical Trials for the Use of Glycolic Acid**

Author/ Year/Rx Duration	Arms/Design	# of Subjects per arm	Indication	Outcome measures	Results
Bari 2002 12 weeks (wks)	<ul style="list-style-type: none"> <li>Group 1=tretinoin X 2 weeks pretreatment</li> <li>Group 2=no pretreatment</li> </ul> Split-face, 6 peels (q 2 wks) Right side (R)=40-60% GA Left side (L)=20-30% Salicylic Acid (SA) Prospective (P), Randomized (R)	20  20	Melasma-all types	Melasma Area and Severity Index (MASI), Lesional area, photos	Moderate to excellent response on both sides, no statistically significant (SS) differences between sides
Burns 1997 22 wks	<ul style="list-style-type: none"> <li>hydroquinone 2% (HQ) + tretinoin 0.05% (T) + GA 10%</li> <li>HQ + T + GA 10% + GA peels: 6 peels (50-68% GA q 3 wks)</li> </ul> P, R	9  10	Post-inflammatory hyperpigmentation (PIHP) in African American subjects	Hyperpigmentation Area + Severity Index (HASI), Chromameter, photos	Significant overall lightening in both groups, no SS differences between groups
Erbil 2007 20 wks	<ul style="list-style-type: none"> <li>Azaleic Acid 20% cream (AA) + Adapalene 0.1% gel (AG) qhs</li> <li>AA + AG + GA peels (20-70% X 8 peels)</li> </ul> P, R	12  16	Epidermal Melasma-Resistant	MASI, photos	MASI scores↓ significantly on both sides, SS difference in favor of peel group at 12-20 wks
Faghihi 2011 12 wks	<ul style="list-style-type: none"> <li>70% GA peels</li> <li>1% tretinoin peels</li> </ul> Split-face, 4 peels (q 2 wks) R, double-blind (DB)	63 (total)	Epidermal and mixed melasma	MASI, photos, tolerance, patient satisfaction	MASI scores↓ significantly on both sides, no SS difference
Garg 2008 6 months	<ul style="list-style-type: none"> <li>GA peels (Group I)</li> <li>GA peels + tretinoin 0.025% cream (Group II)</li> <li>GA peels + HQ 2% (Group III)</li> </ul> Peels=GA 20-45% q 2 wks X 6 then q 4 wks X 3 R, single-blind (SB)	20 20  20	Melasma-all types	MASI, photos, patient assessment	MASI scores↓ significantly in all groups, Group III SS better than Group I at 6 months

Goldman 2010 60 days	<ul style="list-style-type: none"> <li>Vivite Skin care (“partially neutralized glycolic compounds with natural antioxidants”)</li> <li>Cetaphil</li> </ul> R, investigator-masked (IM)	27  9	Photo-aged skin	9-point IGA, Wrinkle scale, patient ratings	No SS difference except for patient ratings
Guevara 2003 12 wks	<ul style="list-style-type: none"> <li>4% HQ+10%GA+Vit C, E+ sunscreen</li> <li>Sunscreen alone</li> </ul> IM	20  15	Epidermal melasma	Mexameter, MASI, Patient Global Assessment (PGA), Investigator Global Assessment (IGA)	SS decrease using study cream (p<0.0001)
Hurley 2002 8 wks	<ul style="list-style-type: none"> <li>4% HQ + GA peels (20-30% q 2 wks)</li> <li>4% HQ alone</li> </ul> Split-face, P	21 (total)	Epidermal and mixed melasma in Hispanic women	MASI, linear analog scale, PGA, photos, mexameter	MASI scores↓ significantly on both sides, no SS difference
Ilknur 2010 6 months	<ul style="list-style-type: none"> <li>GA peels (20-70% q 2 wks X 12)</li> <li>Amino Fruit Acid (AFA) peels (20-60% q 2 wks X 12)</li> </ul> Split-face, R, SB	31 (total)	Epidermal melasma	MASI, photos, tolerance, patient assessment (PA)	MASI scores↓ significantly on both sides, no difference in PA
Kar 2012 12 wks	<ul style="list-style-type: none"> <li>A: Low fluence Q-switched Nd:YAG laser/wk X 12 wks</li> <li>B: GA peels (35-70%) q 2 wks X 12 wks</li> <li>C: High fluence Q-switched Nd:YAG laser/2 wks X 12 wks</li> </ul>	25  25  25	Melasma – all types in Indian subjects	MASI, photos	MASI scores↓ significantly in all groups, A was SS better than B which was SS better than C
Khunger 2004 12 wks	<ul style="list-style-type: none"> <li>1% tretinoin peel</li> <li>70% GA peel</li> </ul> Split-face Peels q wk X 12 weeks	10 (total)	Epidermal and mixed melasma in dark-skinned women	MASI, photos, tolerance, PA	MASI scores↓ significantly on both sides, no SS difference
Kumari 2010 12 wks	<ul style="list-style-type: none"> <li>GA 20–35% peels/2 wks X ≥4 peels</li> <li>trichloroacetic acid (TCA) 10–20% peels/2 wks X ≥4 peels</li> </ul> R	20  20	Epidermal and mixed melasma in Indian women	MASI, photos, tolerance, PA	MASI scores↓ significantly in both treatment groups, no SS difference

Lawrence 1997 3 months	<ul style="list-style-type: none"> <li>70% GA peel</li> <li>Jessners peel</li> </ul> Peels q month X 3 Split-face	16 (total)	Melasma – all types	MASI, photos, chromameter	MASI scores↓ significantly on both sides, no SS difference
Macedo 2006 7 months	<ul style="list-style-type: none"> <li>10% GA+4% HQ plus vehicle peel</li> <li>10% GA+4% HQ plus 70% GA peel</li> </ul> Split-face q15 d x 4 peels; 30 d rest; treatment reversal to opposite side, also q15 d x 4 peels	8 (total)	Melasma	photos	No SS
Oresajo 2008 12 wks	<ul style="list-style-type: none"> <li>Capryloyl salicylic acid peels 5–10%</li> <li>GA peels 20–50% q 2 wk X 6</li> </ul> Split-face, R, SB	50 (total)	Facial hyper-pigmentation + fine lines	6 grade scale for both facial hyper-pigmentation + fine lines	Significant reduction of pigmentation compared to baseline on both sides, no SS difference
Park 2011 6 weeks	<ul style="list-style-type: none"> <li>Q-switched Nd:YAG laser alone</li> <li>same laser + 30% GA peels q 2 wk X 3</li> </ul> Split-face, R, SB	16 (total)	Melasma-mixed type resistant in Korean women	Mexameter, MASI, PA	MASI scores↓ significantly in both groups; combined Rx was SS better than laser alone
Rendon 2008 12 wks	<ul style="list-style-type: none"> <li>Fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05% + 5 GA peels (% and time between peels not described),</li> </ul> Open label	20	Moderate to Severe Melasma	IGA, Success = clear or almost clear	65% (13/20) achieved success at wk 12 P<0.001 vs baseline
Sarkar 2002 18 wks	<ul style="list-style-type: none"> <li>Triple-combination (TC) cream (hydrocortisone acetate 1%, HQ 5%, tretinoin 0.05%)</li> <li>TC cream + GA peels (30-40% q 3 wks X 6)</li> </ul>	20  20	Epidermal melasma in dark-skinned subjects	MASI, photos, tolerance, PA	MASI scores↓ significantly in both groups; combined Rx was SS better than TC cream alone
Seghal 2003 24 weeks	<ul style="list-style-type: none"> <li>10% GA gel qhs + 20-50% GA peels q 3-4 weeks</li> </ul> Open-label	50	Melasma-4 freckles-4 wrinkles-2 scars- 40	Poor, moderate, good or excellent response	Excellent response in 1, Good in 2 with epidermal melasma

Sobhi 2012 Study duration not specified	<ul style="list-style-type: none"> <li>GA 70% peel X 6</li> <li>topical nanosome vitamin C iontophoresis X 6 (time between sessions not described)</li> </ul> Split-face design, SB	14 (total)	Melasma in Type IV-V skin	MASI, photos, PA	MASI scores↓ significantly in both groups; Vit C was SS better than glycolic acid peels
Stiller 1996 22 wks	<ul style="list-style-type: none"> <li>GA 8%</li> <li>L-Lactic Acid 8%</li> <li>vehicle</li> </ul> R, DB, Vehicle-controlled	21 24 22	Moderate photodamage on face + forearms	9 point PGA, PA, tolerance	Significant improvement in both active arms, no SS difference between acids
Teng 1997 26 wks	<ul style="list-style-type: none"> <li>GA 10% + HQ 2%</li> <li>GA 10% + HQ 2% + GA peels (20-70% q 3 wks)</li> </ul> Split-face	10 (total)	Moderate to severe epidermal melasma in Asian women, fine wrinkling	Photos, PA, Clinician assessment, Munsell color chart	Significant improvement on both sides, no SS difference between sides
Teng 1999 12 wks	<ul style="list-style-type: none"> <li>GA 10% + HQ 2% + Kojic acid 2%</li> <li>GA 10% + HQ 2%</li> </ul> Split-face, R	40 (total)	Epidermal melasma in Chinese women	Photos, PA, Clinician assessment of % improvement	Significant improvement on both sides, no SS difference between sides
Vachiramom 2015 12 wks	<ul style="list-style-type: none"> <li>Low fluence Q-switched Nd:YAG laser q wk X 5</li> <li>Same Laser Rx + 30% GA peels</li> </ul> Split-face, SB, R	15 (total)	Melasma in men - mixed type	Colorimeter, mMASI	mMASI ↓ 38% on combined side vs 17% on laser alone side at wk 4, but then both sides worsened (not back to baseline) at wk 8 and wk 12

Source: Reviewer's Table

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

Melasma, hyperpigmentation, and photodamaged skin are not serious or life-threatening diseases/conditions.

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

Yes, there are approved drug therapies for these conditions that have been shown to be effective. See Section II.B.2.a.

## **Conclusions:**

There are no placebo-controlled trials for the use of glycolic acid in the treatment of melasma or other forms of hyperpigmentation. There are, however numerous active controlled trials showing consistently positive results in the treatment of epidermal melasma with glycolic acid, either as a peel or as a topical agent. There is a single vehicle-controlled clinical trial providing some evidence of effectiveness for the mitigation of manifestations of photodamaged skin.

Many of these trials combined the use of glycolic acid with that of other topical medications like retinoids and/or hydroquinone. All of the trials used adjunctive measures like sun protection with sunscreens and protective clothing. There were some clinical trials with negative results; most of these trials were small and have been criticized in the literature for using low concentrations of glycolic acid or having too short a duration of treatment.

Overall, the evidence suggests a role for glycolic acid as a second line treatment for melasma that has failed standard therapy or as an adjunctive treatment to commonly used topical medications. There is also clinical evidence that provides some support for the effectiveness of glycolic acid for the mitigation of manifestations of photodamaged skin.

### **D. Has the substance been used historically as a drug in compounding?**

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

Glycolic acid has been used in clinical practice in the United States since at least the mid 1990s (Stiller et al., 1996).

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

Glycolic acid has been used to ameliorate the appearance of skin aging and to treat various conditions including melasma, other disorders of hyperpigmentation, calluses, keratoses, acne, and psoriasis (Rajaratnam et al., 2010).

#### *3. How widespread its use has been*

The precise extent of use cannot be determined from the available information. However, in addition to the United States, use has been reported in Brazil, Mexico, France, Singapore, Thailand, Korea, India and Turkey (Rajaratnam et al., 2010).

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

Glycolic acid is listed in the British and the European Pharmacopeia. It was not found in the USP-NF or the pharmacopeia of Japan.

## **Conclusions:**

Glycolic acid has been used for a number of dermatologic conditions. The substance has been used in pharmacy compounding in the United States and in other countries for several decades. The extent of

use could not be precisely determined, but in addition to the United States, use has been reported in at least eight countries in disparate parts of the world.

### III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate glycolic acid, up to 70%, for the 503A Bulks List. After considering the information currently available, a balancing of the criteria *weighs in favor* of glycolic acid, up to 70%, being placed on that list for topical use based on the following:

1. Glycolic acid is well characterized in its physical and chemical properties.
2. The safety profile of glycolic acid shows that reported adverse reactions generally appeared to be local, readily manageable, and temporary in duration. The topical use of glycolic acid is mainly associated with burning, erythema, swelling and less commonly, vesiculation, although serious reactions have been reported with the use of products in which glycolic acid was one among several or many components, or concomitant use of other topical products. and some authors did report post-inflammatory hyperpigmentation and rarely, scarring. No information was available on long-term outcomes.

The reports of systemic reactions to products containing glycolic acid were also confounded by the presence of multiple other components in the products and/or the concomitant use of oral or topical agents.

The available information including extensive clinical data accumulated since the 1990s have not raised major safety concerns associated with the use of glycolic acid.

3. There is some evidence available from active controlled clinical trials on the effectiveness of glycolic acid for melasma. There is a single vehicle, controlled clinical trial that provides some evidence of effectiveness for the mitigation of manifestations of photodamaged skin.
4. Glycolic acid has been compounded for use in melasma, other disorders of hyperpigmentation, and photodamaged skin for several decades, and use has been reported in disparate parts of the world.

Based on this information, a balancing of the four evaluation criteria weighs in favor of glycolic acid, up to 70%, for topical use, be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act. Standard of care for use of higher concentrations (20% to 70%) is in-office application by a licensed health care professional.

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Tab 2

Trichloroacetic Acid

Tab 2a

# Trichloroacetic Acid Nominations

# Fagron

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



<b>What is the name of the nominated ingredient?</b>	<b>Trichloroacetic Acid</b>
<b>Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?</b>	Yes, Trichloroacetic Acid is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect.  Lee, Jung Bock, et al. "Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method." <i>Dermatologic surgery</i> 28.11 (2002): 1017-1021.  Resnik, Sorrel S. "Chemical peeling with trichloroacetic acid." <i>The Journal of dermatologic surgery and oncology</i> 10.7 (1984): 549-550.
<b>Is the ingredient listed in any of the three sections of the Orange Book?</b>	The nominated substance was searched for in all three sections of the Orange Book located at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm</a> . The nominated substance does not appear in any section searches of the Orange Book.
<b>Were any monographs for the ingredient found in the USP or NF monographs?</b>	The nominated substance was searched for at <a href="http://www.uspnf.com">http://www.uspnf.com</a> . The nominated substance is not the subject of a USP or NF monograph.
<b>What is the chemical name of the substance?</b>	2,2,2-trichloroacetic acid
<b>What is the common name of the substance?</b>	Acide Trichloracétique; Acidum Trichloraceticum ;Acidum trichloraceticum ;Acidum Trichloroaceticum; Kwas trichlorooctowy; Kyselina trichloroctová; Trichloracetic Acid; Trichloracto rugstis; Trichloressigsäure; Trichloroacé ico, ácido; Triklorietikkahappo ;Triklorättiksyra; Triklórecsav
<b>Does the substance have a UNII Code?</b>	5V2JDO056X
<b>What is the chemical grade of the substance?</b>	No grade
<b>What is the strength, quality, stability, and purity of the ingredient?</b>	Assay: >= 99.0% Identification (IR): Conforms Description: Colorless, crystalline powder Residue on Ignition: <= 0.03% Clarity of Solution: Conforms Melting Point: 54-58 °C Insoluble Matter: <=0.01% Chloride: <= 0.002% Nitrate: <= 0.002% Phosphate: <= 5 ppm Sulfate: <= 0.02% Heavy Metals (as Pb): <= 0.002% Iron: <= 0.001% Substance darkened by H2SO4: Conforms
<b>How is the ingredient supplied?</b>	Crystals
<b>Is the substance recognized in foreign pharmacopeias or registered in other countries?</b>	European Pharmacopoeia (EP) 8 ,AccuPeel (ICN, Hong Kong) ,AccuPeel (ICN, Singapore) ,ATS (Doms-Adrian, Fr.) ,Averuk Bruciaporri (Marco Viti, Ital.) ,Callicida Brum (Brum, Spain) ,CL tre (Nova Argentia, Ital.) ,IL-33 (Istanbul, Turk.) ,Porriver (Ogna, Ital.) ,Tri-Chlor (Gordon, USA) ,Trichloroacetic Acid Solution,Verrupor (Sella, Ital.) ,Wartner S ift (Chefaro, Ger.)
<b>Has information been submitted about the substance to the USP for consideration of monograph development?</b>	No USP Monograph Submission found.
<b>What dosage form(s) will be compounded using the bulk drug substance?</b>	Topical Liquid
<b>What strength(s) will be compounded from the nominated substance?</b>	20-80%
<b>What are the anticipated route(s) of administration of the compounded drug product(s)?</b>	Topical
<b>Are there safety and efficacy data on compounded drugs using the nominated substance?</b>	Pezeshkpoor F, Banihashemi M, Yazdanpanah MJ, Yousefzadeh H, Sharghi M, Hoseinzadeh H. Comparative study of topical 80% trichloroacetic acid with 35% trichloroacetic acid in the treatment of the common wart. <i>J Drugs Dermatol</i> 2012; 11: e66-e69. 23135096 <a href="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&amp;db=PubMed&amp;dopt=Citation&amp;list_uids=23135096">http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&amp;db=PubMed&amp;dopt=Citation&amp;list_uids=23135096</a>
<b>Has the bulk drug substance been used previously to compound drug product(s)?</b>	Yes, used in the topical treatment of warts and for the removal of tattoos and in cosmetic surgery for chemical peeling of the skin.
<b>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</b>	Used in the treatment of warts
<b>What is the reason for use of a compounded drug product rather than an FDA-approved product?</b>	There are FDA approved preparations for warts. Imiquimod and OTC freezing preparations. Imiquimod is FDA approved for genital and perianal warts. Imiquimod cream does not cure warts, and new warts may appear during treatment. Trichloroacetic Acid is effective for genital warts. It has shown to be safe and effective in genital warts that do not respond well to existing treatments. (F. P. Cengiz and N. Emiroglu (2014) An Open, Comparative Clinical Study on the Efficacy and safety of 10% Trichloroacetic Acid and Cryotherapy for Verruca plana Cutan Ocul Toxicol Jun 18:1-5) Over the counter cryotherapy treatments are not feasible due to the area to be treated.
<b>Is there any other relevant information?</b>	All relevant information was expressed in the above questions



## **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**

<b>Ingredient Name</b>	Trichloroacetic Acid
<b>Chemical/Common Name</b>	Trichloroacetic Acid, TCA
<b>Identifying Codes</b>	76-03-9
<b>Chemical Grade</b>	Provided by FDA Registered Supplier/COA
<b>Description of Strength, Quality, Stability, and Purity</b>	Provided by FDA Registered Supplier/COA
<b>How Supplied</b>	Varies based upon compounding requirement
<b>Recognition in Formularies</b> <i>(including foreign recognition)</i>	USP lists as Reagent, BP, Reagent ACS

### **Information on Compounded Bulk Drug Preparation**

<b>Dosage Form</b>	Varies based upon compounding requirement/prescription
<b>Strength</b>	Varies based upon compounding requirement/prescription
<b>Route of Administration</b>	Varies based upon compounding requirement/prescription
<b>Bibliography</b> <i>(where available)</i>	Kuntz R. Sensitization Therapy for Warts. Int J of Pharmaceutical Compounding 2003; 7(4): 266-270. Levine PJ. Chemical Facial Peel Formulations. Int J of Pharmaceutical Compounding 1999; 3(5): 375-377. Cook KK, Cook WR. Chemical Peel of Nonfacial Skin Using Glycolic Acid Gel Augmented with TCA and Neutralized Based on Visual Staging. Dermatologic Surgery 2000; 26: 994-999.
<b>Past and Proposed Use</b>	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.

## PCCA Nomination

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

<b>Ingredient Name</b>	Trichloroacetic Acid
<b>Is it a "bulk drug substance"</b>	Yes
<b>Is it listed in the Orange Book</b>	No
<b>Does it have a USP or NF Monograph</b>	No
<b>Chemical Name</b>	Trichloroacetic acid
<b>Common Name(s)</b>	Trichloroacetic acid, TCA
<b>UNII Code</b>	5V2JDO056X
<b>Chemical Grade</b>	ACS
<b>Strength, Quality, Stability, and Purity</b>	Assay, Description, Melting Point, pH, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
<b>How supplied</b>	Crystals
<b>Recognition in foreign pharmacopeias or registered in other countries</b>	No; Used in four countries
<b>Submitted to USP for monograph consideration</b>	No
<b>Compounded Dosage Forms</b>	Topical Solution or Gel
<b>Compounded Strengths</b>	0.1 – 90%
<b>Anticipated Routes of Administration</b>	Topical
<b>Safety &amp; Efficacy Data</b>	Pezeshkpoor F, et al. Comparative study of topical 80% trichloroacetic acid with 35% trichloroacetic acid in the treatment of the common wart. J Drugs Dermatol. 2012 Nov;11(11):e66-9. [ <a href="http://www.ncbi.nlm.nih.gov/pubmed/23135096">http://www.ncbi.nlm.nih.gov/pubmed/23135096</a> ]

Taner ZM, et al. Therapeutic value of trichloroacetic acid in the treatment of isolated genital warts on the external female genitalia. J Reprod Med. 2007 Jun;52(6):521-5.  
[<http://www.ncbi.nlm.nih.gov/pubmed/17694970>]

Leheta T, et al. Percutaneous collagen induction versus full-concentration trichloroacetic acid in the treatment of atrophic acne scars. Dermatol Surg. 2011 Feb;37(2):207-16.  
[<http://www.ncbi.nlm.nih.gov/pubmed/21269351>]

Kumari R, Thappa DM. Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol. 2010 Jul-Aug;76(4):447.  
[<http://www.ncbi.nlm.nih.gov/pubmed/20657143>]

**Used Previously to compound drug products**

Warts, Chemical Peel

**Proposed use**

Warts, Chemical Peel

**Reason for use over and FDA-approved product**

Treatment failures and/or patient unable to take FDA approved product

**Other relevant information - Stability information**

Study found potency of various concentrations of TCA to be stable in glass amber bottles for 23 weeks in refrigeration  
<http://www.ncbi.nlm.nih.gov/pubmed/2778186>



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: TRICHLOROACETIC ACID ACS REAGENT CRYSTALS  
ITEM NUMBER: 50-1243 CAS: 76-03-9  
LOT NUMBER: C156857 MW: 163.3900000000  
MFG. DATE: 05/01/2013 FORMULA: CCl<sub>3</sub>COOH  
EXPIRATION: 05/01/2015

TEST	SPECIFICATIONS	RESULTS
Assay	>=99.0 %	99.5 %
Chloride	<= 0.002 % max	0.002 % max
Clarity of solution	pass	pass
Description	pass	pass Colorless crystals
Heavy metals	<=0.002 % max <i>COLORLESS OR NEARLY COLORLESS, DELIQUESCENT PLATES, SCALES, OR CRYSTALS; SLIGHT CHARACTERISTIC ODOR; HYGROSCOPIC</i>	0.002 % max
Identification	pass	pass
Insoluble matter	<=0.01 % <i>TEST A 30% SOLUTION WITHIN A 24 HOUR PERIOD TO ENSURE NO APPARENT PARTICLES ARE PRESENT.</i>	0.01 %
Iron	<= 0.001 % max	0.001 % max
Melting point	pass celsius	pass celsius 57.2C
Nitrate	<= 0.002 % max <i>55-58C Or About 60C</i>	0.002 % max
pH	pass	pass 1.7
Phosphate	<=5 ppm max <i>PH OF 0.1 MOLAR AQ SOLUTION 1.2</i> 5 ppm max	5 ppm max
Residue after ignition	<=0.03 % max	0.01 % max
Solubility	pass	pass
Sub's darkened by H <sub>2</sub> SO <sub>4</sub>	pass	pass
Sulfate	<=0.02 % max <i>SOLUBLE IN WATER WITH A CLEAR TO BROWNISH-YELLOW TINT; SOLUBLE IN ALCOHOL</i>	0.02 % max

QC APPROVED  
PRINT DATE: 3/3/2014  
PAGE: 1 of 1

The above test results have been obtained by our supplier or in our quality control laboratory.  
This analysis is not to be construed as a warranty, expressed or implied.

National Community Pharmacists Association

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
Trichloroacetic acid	trichloroacetic acid	Trichloroacetic acid (TCA)	5V2JDO056X (Salt forms have different UNII's?)	From PCCA Database MSDS: Product is 100% by weight and stable.	Crystals; 100% (w/v) Aqueous Solution, 85% (w/v) Aqueous Solution, 50% (w/v) Aqueous Solution, 30% (w/v) Aqueous Solution	Lists as Reagents: P and D in USP, BP, Reagent ACS	Topical Solution	50% and 90%; 100% (w/v), 85% (w/v), 50% (w/v), & 30% (w/v) Aqueous Solutions	Topical	Kuntz R. Sensitization Therapy for Warts. Int J of Pharmaceutical Compounding 2003; 7(4): 266-270, Levine PJ. Chemical Facial Peel Formulations. Int J of Pharmaceutical Compounding 1999; 3(5): 375-377, Cook KK, Cook WR. Chemical Peel of Nonfacial Skin Using Glycolic Acid Gel Augmented with TCA and Neutralized Based on Visual Staging. Dermatologic Surgery 2000; 26: 994-999.	Verruca vulgaris, Verruca plana juvenilis and Verruca plantaris (Warts), necrotising agent, peeling agent, keralytic, desquamation of horny layer of skin. API in SWF Irrigation for use topically by plastic surgeons and dermatologists for facial peels and warts.

Tab 2b

FDA Review of Trichloroacetic  
Acid



DEPARTMENT OF HEALTH & HUMAN SERVICES

---

Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 29, 2016

FROM: Ben Zhang, PhD  
ORISE Fellow, Office of New Drug Products,  
Office of Pharmaceutical Quality

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Products

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Clinical Reviewer, Division of Dermatology and Dental Products

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THROUGH: Julie Beitz, MD  
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Clinical Team Leader, Division of Dermatology and Dental Products

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Edward D. Bashaw, PharmD  
Division Director, Division of Clinical Pharmacology 3, Office of Clinical  
Pharmacology

Frances Gail Bormel, RPh, JD  
Director, Division of Prescription Drugs, OUDLC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Trichloroacetic Acid for Inclusion on the 503A Bulk Drug Substances List

## I. INTRODUCTION

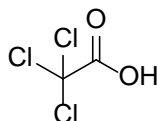
Trichloroacetic acid (TCA) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of common warts (*verrucae vulgaris*) and genital warts (*condylomata accuminata*), as well as for use as a chemical skin peeling agent.<sup>1</sup>

We have reviewed 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 *in favor* of placing trichloroacetic acid for topical use 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).<sup>2</sup>

## II. EVALUATION CRITERIA

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

Yes. TCA is a small organic molecule with the following molecular structure:



It is an analogue of acetic acid. This substance is currently marketed in cosmetics in various dosage forms.

Databases searched for information on TCA in regard to Section II.A of this review include PubMed, SciFinder, Analytical Profiles of Drug Substances, the European

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<sup>1</sup> The proposed use as a *chemical peel* refers to a procedure rather than a recognized medical condition. However, we have considered information about use of TCA as a chemical peel where relevant, including in discussion of reported adverse reactions from use of TCA in conditions potentially related to chemical peels (discussed in section II.B.2.a) and efficacy information from references about chemical peels in the nomination in section II.C.1.

<sup>2</sup> Inclusion on the list of bulk drug substances that can be used in compounding under section 503A (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 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) and (bb)).

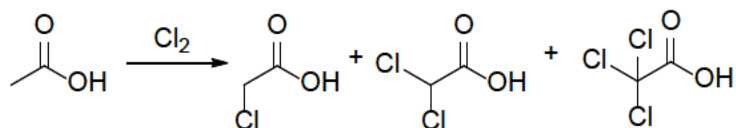
Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopoeia/National Formulary (USP/NF).

1. *Stability of the API and likely dosage forms*

TCA decomposes when heated, especially in basic aqueous solutions (O'Neil et al., 2006; Clark 1959). Decarboxylation also occurs under basic conditions, generating carbonate and chloroform. Under refrigeration, TCA is likely to be stable as topical liquid if the pH of the solution is acidic or neutral.

2. *Probable routes of API synthesis*

Current synthesis of TCA is based mainly on the chlorination of acetic acid (shown below). Acetic acid is reacted with chlorine under anhydrous conditions in the presence of a catalyst. The product is usually a mixture of monochloroacetic acid, dichloroacetic acid, and trichloroacetic acid. TCA is then isolated from the mixture (Pragt et al., 2015).



3. *Likely impurities*

Likely impurities may include:

- Side products or byproducts from the chlorination reaction, such as monochloroacetic acid and dichloroacetic acid
- Residual starting materials, such as acetic acid
- Degradation product of TCA, such as chloroform

4. *Toxicity of those likely impurities*

Chloroform has high toxicity, and monochloroacetic acid and dichloroacetic acid can have toxicities depending on the exposure level. Other impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section II.B.

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

TCA is a colorless crystalline solid that is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability has been 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*

TCA is easily characterized with Carbon-13 nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

**Conclusions:** TCA is a small organic molecule, and it is likely to be stable under refrigeration. The nominated substance 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 public databases were consulted in the preparation of this review: PubMed, Hazardous Substances Data Bank (HSDB), Chemical Abstracts Service (CAPLUS), and Excerpta Medica dataBASE (EMBASE).

- a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

TCA denatures and precipitates proteins.

- b. Safety pharmacology

No information located.

- c. Acute toxicity

The acute oral  $\text{LD}_{50}$  in rats has been reported to be 5000 mg/kg (Bailey and White 1965). TCA is assumed to be neutralized in this study. Data from an internal Hoechst study reports the acute oral  $\text{LD}_{50}$  in rats as ranging from 3310 to 6900 mg/kg and the acute oral  $\text{LD}_{50}$  in dogs as ranging from 1590 to 2000 mg/kg (not otherwise described, assumed to be neutralized TCA; reported in OECD SIDS).

Data from an internal Hoechst study reports the acute dermal  $\text{LD}_{50}$  in rats as >2000 mg/kg (not otherwise described, assumed to be neutralized TCA; reported in OECD SIDS).

Dilute solutions of TCA (<30%) will decompose to produce toxic vapors of chloroform, hydrogen chloride, carbon monoxide and carbon dioxide (Merck Index, 2013). Although the hazard is high (e.g., chloroform is a known central nervous system depressant), the risk is dependent on exposure characteristics (i.e., concentration and duration of exposure). Other potential impurities are dichloroacetic acid (DCA), monochloroacetic acid (MCA), and acetic acid. Although DCA and MCA are progressively more toxic than TCA, these unreacted impurities are unlikely to be present at levels of concern in medical grade TCA.

d. Repeat dose toxicity

No repeat dose dermal toxicity studies for TCA have been located.

Mather et al., (1990) treated male Sprague-Dawley rats (10/dose group) with neutralized TCA in drinking water (0, 50, 500, 5000 ppm; 0, 4.1, 36.5, or 355 mg/kg/day) for 90 days. TCA administration did not affect body weights at any dose. At 355 mg/kg/day, relative liver and kidney weights were significantly ( $p \leq 0.05$ ) increased (7 and 11%, respectively) compared with controls. The liver, spleen and kidney of animals administered this dose were enlarged; however no microscopic lesions were observed at any dose. The NOAEL was determined to be 36.5 mg/kg/day based on statistically increased relative liver and kidney weights at 355 mg/kg/day.

e. Mutagenicity

TCA was non-mutagenic in many strains of *Salmonella typhimurium* (TA98, TA100, TA104, and TA1535) with or without metabolic activation (Rapson et al., 1980; Moriya et al., 1983; Nelson et al., 2001; Kargalioglu et al., 2002). However, positive mutagenicity results have been reported in TA100 and TA1535 strains of *S. typhimurium* (Giller et al., 1997; Ono et al., 1991). Mutagenicity in mouse lymphoma cells was only induced at cytotoxic concentrations (Harrington-Brock et al., 1998). Evaluation of genetic toxicity studies with TCA must consider cytotoxicity and acidification of the medium resulting in precipitation of proteins when interpreting in vitro results. TCA is commonly used as a laboratory reagent to precipitate proteins and terminate enzyme activity. Therefore, it is not surprising that the evidence for its genotoxic potential is inconclusive.

Although positive results were reported for unneutralized TCA during in vivo cytogenetic assays (Bhunya and Behera, 1987), later in vivo studies by Mackay et al. (1995), using neutralized TCA, reported negative results in C57BL/6 mice given two doses 24 hours apart (males: < 1080 mg/kg/dose; females: < 1300 mg/kg/dose). Previous positive reports of TCA-induced clastogenicity may be secondary to pH changes.

f. Developmental and reproductive toxicity

In an embryofetal development study conducted in rats, dams (n=20-21/dose) were administered oral TCA (0, 330, 800, 1200, 1800 mg/kg/day in distilled water, adjusted to pH 7 with NaOH) from days 6 to 15 of gestation (Smith et al., 1989). Maternal and embryonic toxicity were observed from doses of 330 mg/kg/day and above, and embryoletality from doses of 800 mg/kg/day and above. There was a dose-dependent increase in visceral anomalies, particularly in the cardiovascular system. The mean frequency of soft tissue malformations, especially in the cardiovascular system, ranged from 9% at the low dose (330 mg/kg/day) to 97% at the high dose (1800 mg/kg/day). Skeletal malformations were found only at 1200 and 1800 mg/kg/day and were mainly in the orbit. Based

on these observations, TCA was considered to be developmentally toxic in the pregnant rat at doses of 330 mg/kg/day and above.

No developmental and reproductive toxicity studies conducted in rabbits have been located.

g. Carcinogenicity

No carcinogenicity studies conducted with dermal exposure of TCA have been located.

When administered in the drinking water, TCA induced hepatocellular neoplasia in male (De Angelo et al., 2008) and female (Pereira MA, 1996) B6C3F<sub>1</sub> mice. The development of hepatocellular neoplasia in mice exposed to TCA was strongly associated with increased peroxisome proliferation (De Angelo et al., 2008). There is no evidence of carcinogenicity in male F344/N rats (50/group) exposed to TCA (0, 3.6, 32.5, or 364 mg/kg/day) in the drinking water for up to 104 weeks (De Angelo et al., 1997). Peroxisome proliferation was only minimally increased in the TCA-treated rats.

The induction of hepatic tumors by TCA appears to be a species-specific effect, mediated through nongenotoxic mechanisms (Klaunig et al., 1989). The current weight-of-evidence suggests that TCA-induced liver tumors may arise by a peroxisome proliferation-based mechanism of action (Corton 2008).

Under USEPA's Cancer Guidelines, there is suggestive evidence of carcinogenic potential for TCA based on significantly increased incidences of liver tumors in B6C3F<sub>1</sub> mice and lack of treatment-related tumors in a study of male F344/N rats (USEPA 2005). The American Conference of Industrial Hygienists considers TCA to be a confirmed carcinogen in experimental animals with unknown relevance to humans (HSDB 2012).

The International Agency for Research on Cancer (IARC) classifies the hazard of repeat dose oral exposure of TCA as possibly carcinogenic in humans (Group 2B) (IARC, 2014).<sup>3</sup> The possible mechanism for formation of liver tumors in mice (i.e., peroxisome proliferation) does not have clinical relevance. In addition, liver tumors noted in mice occurred after high systemic levels achieved upon oral administration of TCA in drinking water. The systemic levels of TCA achieved after topical administration of TCA under the proposed clinical conditions of use

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<sup>3</sup> This classification is based on "sufficient evidence in experimental animals" (i.e., hepatocellular neoplasia in orally exposed mice and no evidence in similarly exposed rats) and "inadequate evidence in humans" (i.e., no data were available in humans; IARC, 2014). IARC publishes monographs containing critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures to chemicals. The monographs are limited to evaluating cancer hazard (i.e., a chemical's ability to cause cancer under specific circumstances) and do not evaluate risk (i.e., estimate of carcinogenic effects expected from human exposure to a specific chemical).

will not reach the systemic levels of TCA that caused the formation of liver tumors in mice. Therefore, the possible risk of carcinogenesis in humans exposed to TCA after topical administration is minimal based on the available animal data.

#### h. Toxicokinetics

No toxicokinetic studies conducted with dermal exposure of TCA have been located.

In rodents, TCA is rapidly absorbed after oral administration, but is only slowly metabolized, accumulating to a steady-state after successive exposures. Most of the absorbed dose is excreted in the urine as the parent compound. Metabolism that does occur is mainly oxidative through cytochrome P450 to dichloroacetic acid via a dichloroacetic acid radical. The results of several studies indicate that the urinary elimination or plasma clearance of TCA is slower in humans than in rodents (IARC, 2014). Also, protein binding in the plasma is greater in humans than in rodents (Lumpkin et al., 2003). The greater plasma protein binding in humans would be expected to increase the residence time for TCA in plasma and reduce the amount of TCA available in other tissues.

**Conclusions:** No repeat dose dermal toxicity studies or dermal carcinogenicity studies conducted with TCA have been located in the literature. Although the toxicity of TCA after topical administration has not been fully evaluated in nonclinical studies, the available animal data do not pose serious safety issues for topical use in humans.

## 2. *Human Safety*

The following database(s) were consulted in the preparation of this review: PubMed, the Cochrane Library, Federal Register, EMBASE, Web of Science, Micromedex  
Key words: trichloroacetic acid, trichloroethanoic acid.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for trichloroacetic acid (TCA) use through December 14, 2015, and retrieved eleven cases.

Eight cases involved topical application of TCA:

- Six cases reported application site reactions, including pain, erythema, pruritus, inflammation, hypo- and hyperpigmentation, and second degree burns were noted with topical TCA use. The TCA concentration ranged from 20% to 35%. The four cases reporting reaction sites identified the face.
- Two cases reported concomitant use of glycolic acid, topical tretinoin, and bleach. Concomitant treatments included topical and oral agents, and hyperbaric oxygen:

- One case reported fever, urinary retention, dysuria, swelling, application site pain and ulcer associated with genital wart treatment. Signs and symptoms developed after one TCA treatment of unknown strength, followed by three alternate-day imiquimod 5% applications. The patient was hospitalized, catheterized, and treated with prednisone.
- One case reported severe glabellar injection site pain and tenderness after onabotulinumtoxinA injection, associated with a TCA 20% chemical peel. The order of administration was not specified.

Three cases involved other or unspecified routes of administration of TCA:

- One case reported elevated creatine phosphokinase, myositis, and rhabdomyolysis after use of an unspecified TCA product and an unspecified dose of simvastatin. The route and indication of TCA use were not specified. The patient improved with discontinuing both TCA and simvastatin, and hydration.
- One case reported intentional Tri-Chlor solution (TCA 80%) ingestion, along with clonazepam, amlodipine, and metoprolol in an attempted suicide. Tachycardia, lethargy, slurred speech, hyperglycemia, and hypotension were noted. The patient recovered.
- One case reported elevated concentrations of TCA, trichloroethanol, chloral hydrate, and other substances in a positive toxicology screen performed in a deceased, multiple-drug overdose patient. TCA and trichloroethanol are chloral hydrate metabolites. The substances ingested were not identified.

FDA's Center for Food Safety and Nutrition was also consulted to search their adverse event data base (CAERS) for adverse events associated with TCA and retrieved no relevant cases.

a. Reported adverse reactions

Genital Warts. Table 1 shows adverse reactions from TCA use in genital wart treatment as reported in the literature.

**Table 1. Adverse Reactions from TCA Use in Genital Wart Treatment**

<u>Reference</u>	<u>Study Design</u>	<u>TCA Strength</u>	<u>Dosing Regimen</u>	<u>AR rate and type in TCA-treated subjects</u>
Gabriel et al., 1983	TCA + 25% podophyllin vs 25% podophyllin in males	50%	1x/wk for up to 6 wks	5/31 (16%); ulceration (3), soreness (2)
Godley et al., 1987	TCA vs cryotherapy in males	unknown	1x/wk for up to 10 wks	3/57 (5%) mild discomfort, 26/57 (46%) ulceration
Abdullah et al., 1993	TCA vs cryotherapy	95%	1x/wk for up to 6 wks	9/33 (27%); ulceration (9)
Nunns et al., 1996	Case report of 2 cases	unknown	Two weekly treatments	Severe vestibulitis with erythema and tenderness up to 15 wks, and one case of posterior fourchette fissures
Schwartz et al., 1998	Retrospective record review of pregnant women: TCA used in combination with CO2 laser	85%	unknown	7/32 (22%) “extensive vulvar ablation” requiring suprapubic catheterization, 2/32 (6%) mild uterine contractions, 3/32 (9%) spontaneous rupture of membranes, 1/32 (3%) depigmentation
Sherrard et al., 2007	Randomized 5-arm study	unknown	2x/wk for up to 8 wks	0/173
Taner et al., 2007	Uncontrolled study of TCA in females	85%	1x/5days for up to 6 sessions	51/51 (100%) transient burning pain, 8/51 (16%) ulceration with permanent scarring in 3 subjects (6%)

Common Warts. Table 2 shows adverse reactions from TCA use in common wart treatment as reported in the literature.

**Table 2. Adverse Reactions from TCA Use in Common Wart Treatment**

<b><u>Reference</u></b>	<b><u>Study Design</u></b>	<b><u>TCA Strength</u></b>	<b><u>Dosing Regimen</u></b>	<b><u>AR rate and type in TCA-treated subjects</u></b>
Pezeshkpoor et al., 2012	TCA 80% vs TCA 35%	80% and 35%	1x/wk for up to 6 wks	9/31 (29%) with TCA 80%, and 5/31 (16%) with TCA 35%: burning sensations, tingling, local pain, scarring and hyperpigmentation
Silverberg et al., 2012	retrospective chart review of children comparing (a) SADBE*, (b) SADBE + TCA, (c) SADBE + TCA + cantharidin, (d) SADBE + cantharidin	50%	TCA 1-2 min immediately prior to SADBE; cantharidin 1-2 min immediately after SADBE	No adverse effects attributed to TCA
Cengiz et al., 2015	TCA 25% vs TCA 10% vs liquid nitrogen in flat warts	25% and 10%	1x/5days for up to 6 treatments	TCA 25% group (N=27): pruritus 78%, pain 26%, erythema 37%; TCA 10% group (N=28): pruritus 50%, pain 4%, erythema 7%

\*SADBE = squaric acid dibutylester

**b. Other conditions**

- Acne and Acne Scars

Meguid et al., (2015) conducted an inpatient comparison study of TCA 25% versus salicylic acid 30% for mild to moderate facial acne vulgaris. Twenty patients were pretreated with retinoic acid 0.1% cream. TCA and salicylic acid were then consistently applied, each to one side of the face every 2 weeks for 2 months. Prolonged erythema occurred only with the TCA side in 5 (25%) of the subjects. Hyperpigmentation was reported by 4 patients (20%) due to TCA application, which lasted 3 to 4 weeks and resolved with a “topical bleaching agent.”

Lee et al. (2002) compared TCA 65% to TCA 100% using the chemical reconstruction of skin scars (CROSS) technique in treatment of acne scars. The CROSS method consists of the focal application of concentrated TCA with a sharpened wooden applicator by applying firm pressure to the depressed scar area. For 65 subjects, “mild erythema” and “transient postinflammatory hyperpigmentation” were reported; the number of patients reporting the adverse effects was not given. Four subjects developed “mild pustular eruptions” which cleared after oral antibiotic treatment.

Nofal et al., (2014) studied treatment of acne scars in 45 patients assigned to three groups: TCA 100% applied via CROSS technique; autologous platelet-rich plasma injection; combined skin needling and autologous topical platelet-

rich plasma. In the TCA group, all subjects experienced mild pain, and four patients developed hyperpigmentation.

Leheta et al., (2011) compared TCA 100% via CROSS technique to percutaneous collagen induction (PCI) to treat acne scars. The PCI procedure uses skin needling penetration of the epidermis to stimulate wound healing, collagen deposition, and tissue remodeling. All 15 TCA subjects noted burning pain, crusting, and erythema. Also, 50% of subjects completing TCA treatment developed hyperpigmentation which lasted 2 to 6 months.

- Hyperpigmented Lesions

Hong et al., (2012) conducted a split-face study comparing TCA 15% chemical peel to 1550 nm fractional photothermolysis for facial melasma. Treatments were administered during one session. Eighteen women were treated. Persistent erythema and hyperpigmentation occurred in 9 (50%) of TCA subjects and 8 (44%) of laser subjects.

Kumari et al., (2010) compared TCA (10% or 20%) with glycolic acid (GA) (20% or 35%) chemical peels to treat melasma. The 2-week, priming regimen for the TCA group was tretinoin 0.1% gel daily, and for the GA group was GA 12% cream daily. Forty subjects were treated with chemical peels, with graded concentrations and 2- or 4-minute contact times. Subjects were treated every 15 days. Of 20 subjects treated in each group, subjects treated with TCA experienced less “mild burning” compared to glycolic acid, but more “postpeel crackening.”

Soliman et al., (2007) compared TCA 20% chemical peel alone (15 women) to TCA 20% with ascorbic acid 5% chemical peel (15 women) to treat melasma. All patients were primed for two weeks with tretinoin 0.05% gel daily and hydroquinone 4% cream daily. Also, the TCA/ascorbic acid group applied ascorbic acid compounded in cold cream daily. TCA chemical peels were performed weekly until clear or up to six treatments. Erythema was reported in 30% of TCA alone patients and 20% of TCA/ascorbic acid patients. “Discomfort” was reported in 25% of patients in both groups. Acne was noted in one patient in the TCA/ascorbic acid group.

Fung et al., (2002) reported one case of TCA 35% facial peel to treat dyschromia and for rejuvenation causing corneal punctate keratitis and conjunctival infection.

Raziee et al. (2008) compared TCA 33% solution with cryotherapy within subject to treat solar lentigines. TCA and liquid nitrogen were applied to the dorsal hands of 25 women. Postinflammatory hyperpigmentation was reported in 11 (44%) of TCA applications compared to 10 (40%) of cryotherapy treatments.

- Actinic Keratosis

Lawrence et al., (1995) conducted a split-face study comparing Jessner's solution followed by TCA 35% chemical peel to fluorouracil 5% cream application to treat actinic keratoses. Fourteen of 15 subjects reported erythema for the side treated by Jessner's/TCA chemical peel, which persisted for 3 months in one subject.

- Xanthelasma

Haque et al., (2006) compared TCA 100%, 70% and 50% strengths for treatment of eyelid xanthelasma. Fifty-one subjects were treated every 2 weeks until lesions cleared. Follow up visits were scheduled once a month. With TCA application, there was white discoloration immediately with "peri-lesional erythema" that subsided in a few hours, followed by a "dark, brownish-black crust". Follow up visits reported 11 patients with hypopigmentation (four treated with TCA 100%, three treated with TCA 70% and four patients treated with TCA 50%). Five patients developed hyperpigmentation (three patients treated with TCA 100% and two patients treated with TCA 70%). One patient developed "mild scarring", not defined, after TCA 100% treatment.

Nahas et al., (2009) studied TCA 70% for eyelid xanthelasma in 24 subjects. Adverse events noted were "scar practically invisible" in 11 patients (45.8%), "presence of mild dyschromia" (hypopigmentation and hyperpigmentation) reported in 8 patients (33.4%), and "marked dyschromia or alteration of relief" in 5 patients (20.8%).

Güngör et al., (2014) conducted an inpatient comparison study of TCA 70% with erbium: YAG laser treatment in 21 patients with eyelid xanthelasma. Treatments were 4 weeks apart, if needed. Follow up evaluation occurred 4 weeks after the first treatment by two independent dermatologists. Improvement and adverse effects were assessed by scoring system. Over 50% of patients treated with TCA and laser noted "mild discoloration," and over 30% reported "marked discoloration"; there was no statistically significant difference between the treatments.

c. Clinical trials assessing safety

There have been no clinical trials specifically designed to address the safety of TCA. Safety assessments were among the study procedures in several clinical trials. The safety profile of TCA in these trials was consistent with that provided in the reports cited above. See Section II.B.2.a.

d. Pharmacokinetic data

There are no reports of human pharmacokinetic (PK) studies following topical application of TCA.

e. The availability of alternative approved therapies that may be as safe or safer.

FDA approved therapies for warts include the following.

Prescription:

- Imiquimod 5% cream and 3.75% cream for genital warts
- Podofilox 0.5% gel and solution for external genital warts
- Sinecatechins 15% ointment for external genital warts
- Interferon alfa-2b intralesional injection for genital warts

There are no approved prescription therapies for warts outside of the genital area.

Non-prescription:

- Salicylic acid 5 % to 40% topically for common and plantar warts is subject to the final monograph Miscellaneous External Drug Products For Over-The-Counter Human Use - Wart Remover Drug Products (21 CFR 358 subpart B).
- Cryosurgical system/kit (dimethyl ether and propane) to freeze common and plantar warts, indicated for ages 4 years and up

Other widely used therapies for warts include procedural therapies, such as cryotherapy; laser therapy; electrosurgery; surgical excision; and duct tape occlusion.

**Conclusions:**

1. Clinical data from the use of TCA in the treatment of genital and common warts show that adverse reactions secondary to TCA (concentration 10% to 100%) application included burning, pain, erythema, hyperpigmentation and hypopigmentation. More serious adverse reactions reported were ulcerations, scarring, pustules, punctate keratitis and conjunctival infection. Adverse events were reported more frequently with higher concentrations.
2. Ulcerations were reported in most studies with wart treatment in the genital area. For localized wart involvement, scars or hypopigmentation were the most frequent sequelae. With more extensive genital wart treatment, requirement for suprapubic catheterization has been reported (catheterization reported in FAERS and in literature). Also, urinary retention was reported.
3. Other FDA approved therapies are available to treat genital warts and common warts. We have not been able to locate clinical trials directly comparing TCA and FDA-approved treatments for warts.

### C. Are there concerns about whether a 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*

#### External genital warts

Abdullah et al., (1993) compared topical TCA 95% (N=33) to liquid nitrogen (N=53) cryotherapy in the treatment of external genital warts with once weekly application for up to 6 treatments. In the TCA group, lesions were cleared in 64% of subjects, compared to 70% of subjects in the liquid nitrogen group.

Gabriel et al., (1983) compared TCA 50%, in combination with podophyllin 25%, to podophyllin 25% alone to treat genital warts with once weekly treatment for 6 weeks and follow-up for at least 3 months after initial treatment. For subjects treated with TCA/podophyllin, 20 (69%) of 29 subjects were cleared of lesions at week 6, and 9 (31%) subjects were cleared of lesions at 3 months. In the podophyllin alone group, 21 (60%) of 35 subjects were cleared of lesions at 6 weeks, and 10 (29%) subjects were cleared of lesions at 3 months.

Godley et al., (1987) compared treatment of genital warts in men with TCA (of unknown concentration) (N=57) to liquid nitrogen cryotherapy (N=49), with TCA applied weekly for up to 10 treatments. At week 10, 46 (81%) subjects in the TCA group, and 43 (88%) subjects in the cryotherapy group had complete clearance of lesions. Of patients cleared of lesions who returned for follow up 2 months after the last treatment, lesions recurred in 14 (36%) of 39 subjects in the TCA group, and in 15 (40%) of 38 subjects in the cryotherapy group.

Sherrard et al., (2007) compared treatment with TCA (of unknown concentration) followed by podophyllin 25% (N=85), TCA alone (N=88), podophyllin 25% alone (N=79), cryotherapy alone (N=81), and cryotherapy followed by podophyllin 25% (N=76), with once a week treatment for up to 8 weeks. The efficacy endpoint was complete clearance of all lesions. The results are as follows:

- Complete clearance of lesions was reported in 49 (56%) subjects treated with TCA alone and in 63 (74%) subjects treated with TCA/podophyllin combination therapy. In the cryotherapy alone treatment group, complete clearance was reported in 61 (75%) subjects compared to 59 (78%) subjects in cryotherapy/podophyllin treatment group. In the podophyllin alone treatment group, complete clearance was reported in 46 (58%) subjects.
- Persistent lesions were reported for 10 (13%) subjects treated with podophyllin alone, 9 (10%) subjects treated with TCA alone, 5 (6%) subjects treated with cryotherapy alone, 2 (2%) subjects treated with TCA/podophyllin and none (0%) of the subjects treated with the cryotherapy/ podophyllin combination.

Taner et al., (2007) conducted an open label trial with TCA 85% application to genital warts in 51 female subjects. TCA was applied every 5 days until all lesions cleared, or

up to 6 treatments. Subjects were followed-up in 2-month intervals for 6 months. Follow-up was extended for an additional 6 months for a subset of these subjects.

- Complete clearance of all lesions was reported in all subjects by the end of the fifth cycle. At the end of first 6-month follow-up, no recurrence was reported.
- At the end of the second 6-month follow-up period, 9 subjects (18%) had recurrent lesions. Of these subjects, 3 subjects reported lesions in areas treated with TCA, and 6 subjects had developed new lesions.

### **Common Warts**

Pezeshkpoor et al., (2012) compared TCA 80% with TCA 35% to treat common warts. Fifty-five subjects were included in the final analysis after treatment with TCA once a week for up to 6 weeks, and followed up weekly up to the end of week 7 (N=30 for TCA 80% and N=25 for TCA 35%). All subjects were evaluated for recurrence after 12 weeks. A “good” response was defined as fewer than or equal to 3 warts remaining. In the TCA 80% group, 14 subjects (47%) had a good response, while 3 subjects (12%) in the TCA 35% group had a good response. However, since the number of subjects completely cleared of wart lesions was not reported, this study is essentially uninformative.

Cengiz et al., (2015) conducted an open, comparative clinical trial for flat warts (*verruca plana*) in three arms: TCA 10% (N=28); TCA 25% (N=27); cryotherapy (N=25), with weekly treatment for up to 8 weeks, and evaluation every 2 weeks. There was no follow up beyond treatment week 8. In the TCA 10% group, 24 subjects (85.7%) cleared of warts completely by 8 weeks, while for those treated with TCA 25%, 25 (92.6%) subjects’ wart lesions cleared, and with cryotherapy, 23 (92%) subjects’ wart lesions cleared.

In 2008, Patidar reported one case of 2 periungual warts on the hands treated by electrodesiccation and curettage, followed by TCA 30% application. There was no recurrence after one year.

### **Chemical Skin Peeling**

One of the nominations included two references for TCA potentially related to its use as a chemical peel: Leheta et al. (2011) on atrophic acne scars and Kumari and Thappa (2010) on melasma. Note that TCA was not nominated as a treatment for scarring or melasma, and we consider these studies to the extent they are relevant for consideration of the chemical peel nomination.

- Atrophic acne scars

Leheta et al., (2011) compared percutaneous collagen induction (PCI) and 100% TCA chemical reconstruction of skin scars (CROSS) method for the treatment of atrophic acne scars. The CROSS method is a focal application of TCA 100% to atrophic acne scars. The study included 30 subjects randomly divided (1:1) into two groups: group 1

underwent 4 sessions (4 weeks apart) of PCI, and group 2 similarly with 100% TCA CROSS. Acne scarring improved in all subjects. Scar severity scores improved by a mean of 68.3% from baseline ( $p < 0.001$ ) in group 1 and 75.3% ( $p < 0.001$ ) in group 2, but improvement was not statistically significant between the groups ( $p = 0.47$ ).

Besides the study described above, two other trials evaluated the use of TCA CROSS in acne scars (Lee et al. (2002), and Nofal et al. (2014)). Both studies showed improvement of the atrophic acne scars from baseline after TCA peel. Similar to the Leheta study, the comparators are not approved therapies, and no conclusions can be drawn regarding efficacy of TCA CROSS in acne scars.

- Melasma

Kumari and Thappa (2010) compared the response of melasma in 40 Indian women with a minimum melasma area and severity index (MASI) of 10 to glycolic acid (GA) versus TCA for chemical peeling. Study subjects had a pre-peel program of daily application of 12% GA cream or 0.1% tretinoin at night for 2 weeks. They were then treated with graded concentrations of 20-35% GA facial peel every 15 days in the GA group and 10-20% TCA in the TCA group. Reduction in MASI after 12 weeks was by 79% in the GA group and by 73% in the TCA group (difference not significant). Patients with epidermal-type melasma showed better response than those with mixed-type melasma ( $P < 0.05$ ). Subject evaluation was “good” or “very good” in 75% of the women of the GA group and 65% of the TCA group. No relation of treatment response to age or duration of melasma could be established.

Besides the study described above, two other trials evaluated the use of TCA peel in melasma (Hong et al., (2012), and Soliman et al. (2007)). Both studies showed improvement of melasma from baseline after TCA peel. However, similar to the Kumari study, the comparators are not approved drug therapies, and no conclusions can be drawn regarding efficacy of TCA peel in melasma.

2. *Whether or not the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

No, common and genital verrucae are not serious or life-threatening diseases/conditions in healthy persons; however, there are less common circumstances in which warts may develop into extensive, recalcitrant infections, premalignancies, and carcinomas.

3. *Whether or not there are any alternative approved therapies that may be as effective or more effective.*

We address alternative therapies for warts here. Chemical peel involves a variety of procedures used for multiple purposes, and it is not possible to address alternatives in the current context without specific proposed uses.

There are approved drug therapies for warts that have been shown to be as effective or more effective. According to several studies (Abdullah et al., 1993; Sherrard et al.,

2007), other treatments and combinations are superior to TCA alone, although TCA may be useful as an adjunctive, destructive therapy.

For a list of approved therapies for the treatment of external genital warts and common warts, see section II.B.2.d.

### **Conclusions:**

1. We did not identify adequate and well-controlled clinical trials evaluating TCA efficacy in the treatment of genital or common warts. The available information suggests that TCA may be efficacious in the treatment of these conditions; however, the limited data are from small, open-label, active controlled trials, or a case report.
2. Some of the trials presented above evaluated efficacy of TCA in combination with other wart treatments (e.g., cryotherapy, podophyllin). One report suggested an increase in TCA efficacy when used in combination with podophyllin (Sherrard et al., 2007). Some reports (Cenzig et al., 2015, Pezeshkpoor et al., 2012) suggested an increase in efficacy of TCA therapy for common or flat warts at higher concentrations. However, even with higher TCA concentrations, current data do not suggest an advantage in efficacy of TCA alone over available approved or over-the-counter treatments for warts.

### **D. Has the substance been used historically as a drug in compounding?**

Databases searched for information on TCA in regard to Section D of this consultation included PubMed, Natural Medicines Database, clinicaltrials.gov, Google, European Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia.

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

TCA has been used for treating warts and as a chemical peel for over 40 years (Heaumebh, 1964, Resnick et. al., 1973). From the literature, it appears that TCA has been used in pharmacy compounding for at least 20 years. (Bridenstine 1996, Bridenstine et. al., 1994).

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

TCA has been used to treat dermatologic conditions including warts, actinic keratoses, melasma, solar lentigines, acne, acne scarring, and xanthelasma. However, it is not clear to what extent TCA has been used in the treatment of these conditions either in marketed product formulations or via pharmacy compounding.

3. *How widespread its use has been*

TCA has been used to treat warts in the United States and internationally. Insufficient data are available from which to draw conclusions about the extent of use of TCA in compounded drug products.

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

TCA and TCA solution are listed in the European Pharmacopeia (8<sup>th</sup> Edition, 2016, 8.8) and the British Pharmacopoeia (BP 2016). Per the British Pharmacopoeia, TCA solution is a cutaneous solution used in the treatment of warts, although it is not currently licensed in the United Kingdom. TCA is not listed in the Japanese Pharmacopoeia (17<sup>th</sup> Edition).

**Conclusions:** TCA has been used to treat warts for over 40 years and there is evidence of its use in pharmacy compounding for at least 20 years. TCA and TCA solution have official recognition in other countries.

### III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate TCA for the 503A Bulks List. In the Agency's view, after considering the information currently available, a balance of the criteria weighs *in favor* of TCA for topical use being placed on the list based on the following:

1. TCA is well characterized in its physical and chemical properties.
2. The safety profile shows that TCA commonly causes erythema, crusting, hyperpigmentation and hypopigmentation, burning, and pain at the application site. More adverse effects have been reported upon use of TCA at higher concentrations, as well as in the facial and genital areas. At higher concentrations, the potential for ulceration and subsequent absorption through open wounds increases. Ulcerations have been reported in most studies of TCA in the treatment of genital warts.
3. Although we did not identify adequate and well-controlled trials evaluating TCA efficacy in the treatment of warts, available information from small open label trials suggests that TCA may have some efficacy in their treatment. Studies suggest that TCA is more efficacious when used at higher concentrations or in conjunction with an additional wart treatment and, thus, may have a place in treating refractory warts or patients intolerant of other therapies. However, with higher concentrations, the potential for ulceration and subsequent absorption through open wounds increases.
4. TCA has been used for dermatologic conditions for over 40 years and for at least 20 years in pharmacy compounding. Its use is worldwide.

Based on the information the agency has considered, a balancing of the four evaluation criteria weighs in favor of TCA for topical use being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act.

Because of the potential for complications when used at high concentrations, the standard of care is in-office application by a licensed health care professional.

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## ACRONYM LIST

CEBS	Chemical Effects in Biological Systems
CROSS	Chemical reconstruction of skin scars
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No-Observed-Adverse-Effect Level
PCI	Percutaneous collagen induction

Tab 3

Kojic Acid

Tab 3a

Kojic Acid Nominations

# Fagron

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



## What is the name of the nominated ingredient?

## Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?

### Kojic Acid

Yes, Kojic Acid 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 Kojic Acid pharmacological actions are provided Draelos ZD, Yatskayer M, Bhushan P, Pillai S, and Oresajo C. Evaluation of a kojic acid, emblica extract, and glycolic acid formulation compared with hydroquinone 4% for skin lightening. *Cutis*. 2010;86(3):153-8.

Mohammadpour M, Behjati M, Sadeghi A, and Fassihi A. Wound healing by topical application of antioxidant iron chelators: kojic acid and deferiprone. *Int Wound J*. 2013;10(3):260-4. doi:10.1111/j.1742-481X.2012.00971.x.

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Deo KS, Dash KN, Sharma YK, Virmani NC, and Oberai C. Kojic Acid vis-a-vis its Combinations with Hydroquinone and Betamethasone Valerate in Melasma: A Randomized, Single Blind, Comparative Study of Efficacy and Safety. *Indian J Dermatol*. 2013;58(4):281-5. doi:10.4103/0019-5154.113940.

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Cotellessa C, Peris K, Onorati MT, Fagnoli MC, and Chimenti S. The use of chemical peelings in the treatment of different cutaneous hyperpigmentations. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 1999;25(6):450-454.

Lim J. Treatment of Melasma Using Kojic Acid in a Gel Containing Hydroquinone and Glycolic Acid. *Dermatologic Surgery*. 1999. Available at: <http://www.blackwell-synergy.com/doi/abs/10.1046/j.1524-4725.1999.08236.x>.

<b>Is the ingredient listed in any of the three sections of the Orange Book?</b>	The nominated substance was searched for in all three sections of the Orange Book located at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm</a> . The nominated substance does not appear in any section searches of the Orange Book.
<b>Were any monographs for the ingredient found in the USP or NF monographs?</b>	The nominated substance was searched for at <a href="http://www.uspnf.com">http://www.uspnf.com</a> . The nominated substance is not the subject of a USP or NF monograph.
<b>What is the chemical name of the substance?</b>	5-Hydroxy-2-hydroxymethyl-4-pyrone
<b>What is the common name of the substance?</b>	Kójico, ácido
<b>Does the substance have a UNII Code?</b>	6K23F1TT52
<b>What is the chemical grade of the substance?</b>	no grade
<b>What is the strength, quality, stability, and purity of the ingredient?</b>	Melting Point: 153.0°C - 158.0°C Heavy Metals: ≤ 20 ppm Arsenic: ≤ 2 ppm Loss on Drying: ≤ 0.6% Residue on Ignition: ≤ 0.2% Purity: ≥ 98.0% Total Microbial Count: < 100 cfu/g Pathogenic Bacteria: NIL
<b>How is the ingredient supplied?</b>	Powder
<b>Is the substance recognized in foreign pharmacopeias or registered in other countries?</b>	AHA Skin Lightening Gel (Therapeutic-Ocean, Singapore) ,Alastik (Grunenthal, Chile) ,Biolite (Biosciences Pharmakon, India) ,Brunex (Pentamedical, Ital.) ,Carofit (Ajanta, India) ,Cellskinlab Phyto Spot (Dispolab, Arg.) ,Clearz (Reddy, India) ,D 4 (Fouchard, Chile) ,Demelan (Glenmark, India) ,Despigmentante (Dermoteca, Port.) ,Disco (Floxia, Singapore) ,E-Cate (Captab, India) ,Fade Cream (Cosmofarma, Port.) ,Glyaha-KOJ (Shalaks, India) ,Hidrogel (Roi Surya, Indon.) ,High Potency Lightening Serum (Ocean Health, Singapore) ,KC-Lite (Biomedica, India) ,Melani-D (Roche-Posay, Chile) ,Melani-D Maos (Roche-Posay, Braz.) ,Melasoft (Forder, Arg.) ,Neoquin (Cassara, Arg.) ,NeoStrata (Medstyle, Chile) ,Nova Derm Facial Lightening (Darier, Mex.) Phyto Spot (Dispolab, Chile) ,Primacy Phyto + (Dispolab, Chile) ,Recover OI (Dispolab, Chile) ,Unitone 4 (D & M, Chile)
<b>Has information been submitted about the substance to the USP for consideration of monograph development?</b>	No USP Monograph submission found.
<b>What dosage form(s) will be compounded using the bulk drug substance?</b>	Cream and Gel
<b>What strength(s) will be compounded from the nominated substance?</b>	1 - 5%
<b>What are the anticipated route(s) of administration of the compounded drug product(s)?</b>	Topical

**Are there safety and efficacy data on compounded drugs using the nominated substance?**

Brtko J, Rondahl L, Ficková M, Hudecová D, Eybl V, and Uher M. Kojic acid and its derivatives: history and present state of art. *Cent Eur J Public Health*. 2004;12 Suppl:S16-8.

Bentley R. From miso, saké and shoyu to cosmetics: a century of science for kojic acid. *Nat Prod Rep*. 2006;23(6):1046-62. doi:10.1039/b603758p.

Burnett CL, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Final report of the safety assessment of Kojic acid as used in cosmetics. *Int J Toxicol*. 2010;29(6 Suppl):244S-73. doi:10.1177/1091581810385956.

Mitani H, Koshiishi I, Sumita T, and Imanari T. Prevention of the photodamage in the hairless mouse dorsal skin by kojic acid as an iron chelator. *Eur J Pharmacol*. 2001;411(1-2):169-174.

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Mohammadpour M, Behjati M, Sadeghi A, and Fassihi A. Wound healing by topical application of antioxidant iron chelators: kojic acid and deferiprone. *Int Wound J*. 2013;10(3):260-4. doi:10.1111/j.1742-481X.2012.00971.x.

Pérez-Bernal A, Muñoz-Pérez MA, and Camacho F. Management of facial hyperpigmentation. *Am J Clin Dermatol*. 2000;1(5):261-8.

Garcia A, and Fulton JE. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg*. 1996;22(5):443-7.

Deo KS, Dash KN, Sharma YK, Virmani NC, and Oberai C. Kojic Acid vis-a-vis its Combinations with Hydroquinone and Betamethasone Valerate in Melasma: A Randomized, Single Blind, Comparative Study of Efficacy and Safety. *Indian J Dermatol*. 2013;58(4):281-5. doi:10.4103/0019-5154.113940.

**Has the bulk drug substance been used previously to compound drug product(s)?**

Cream and Gel

**What is the proposed use for the drug product(s) to be compounded with the nominated substance?**

Kojic Acid has been shown effective in the treatment of hyperpigmentation A.F Alexis and P. Blackcloud(2013) *Natural Ingredients for Darker Skin Types: Growing Options for Hyperpigmentation J. Drugs Dermatol Sep;12(9 Suppl):s123-7*

**What is the reason for use of a compounded drug product rather than an FDA-approved product?**

No FDA approved Kojic Acid preparation. Kojic is used for disorders of the skin. Hyperpigmentation is a concern for many individuals. The FDA approved preparation Tri Luma (Fluocinolone, Hydroquinone, and tretinoin) is available for hyperpigmentation. It has had issues with backorders and side effects of rash, blisters, skin bumps, tiny red lines or blood vessels showing, and gradual blue black darkening of skin. Kojic acid is found to have effects alone but much better in combination with FDA approved ingredients such as Hydroquinone for hyperpigmentation disorders. Advantages are to create synergy and allow for lower dosing of other ingredients which can lead to decreased side effect profiles.

**Is there any other relevant information?**

All relevant information was expressed in the above questions

National Community Pharmacists Association											
Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopelas	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
Kojic acid	5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one; 5-hydroxy-2-hydroxy-methyl-4-pyrone	Kojic acid	6K23F1TT52	From PCCA MSDS 100% by weight and unstable.	Powder	Not USP unless by another name	Gel Peel Solution Cream Lotion Solution	0.05% 1% 2% 3% 4% 5% 6% 8% 10%	Topical		topical exfoliant, chelating agent



## **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**

<b>Ingredient Name</b>	Kojic Acid
<b>Chemical/Common Name</b>	5-Hydroxy-2(hydroxymethyl)-4H-pyran-4-one; 5-Hydroxy-2-hydroxy-methyl-4-pyrone
<b>Identifying Codes</b>	501-30-4
<b>Chemical Grade</b>	Provided by FDA Registered Supplier/COA
<b>Description of Strength, Quality, Stability, and Purity</b>	Provided by FDA Registered Supplier/COA
<b>How Supplied</b>	Varies based upon compounding requirement
<b>Recognition in Formularies</b> <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

### **Information on Compounded Bulk Drug Preparation**

<b>Dosage Form</b>	Varies based upon compounding requirement/prescription
<b>Strength</b>	Varies based upon compounding requirement/prescription
<b>Route of Administration</b>	Varies based upon compounding requirement/prescription
<b>Bibliography</b> <i>(where available)</i>	

**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.

Tab 3b

# FDA Review of Kojic Acid



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 29, 2016

FROM: Ben Zhang, PhD  
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Frances Gail Bormel, RPh, JD  
Director, Division of Prescription Drugs, Office of Unapproved Drugs and Labeling Compliance

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Kojic Acid for Inclusion on the 503A Bulk Drug Substances List

## I. INTRODUCTION

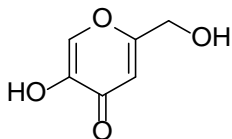
Kojic acid, 0.05 to 10%, has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of hyperpigmentation. It also was nominated as a “chelating agent” and as a “topical exfoliant.” FDA evaluated the potential use of kojic acid as an iron chelator in wound healing and photodamage prevention since references were provided in support of those uses. FDA did not evaluate the potential use of kojic acid as a topical exfoliant since no reference was provided in support of its use as a topical exfoliant.

We have reviewed 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 kojic acid 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).<sup>1</sup>

## II. EVALUATION CRITERIA

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

Kojic acid is a small organic molecule with formula of C<sub>6</sub>H<sub>6</sub>O<sub>4</sub> and molecular weight of 142.11 Gm/mole. It is a naturally occurring chelation agent. This compound is currently marketed for cosmetic use in creams, lotions, gel peels, and in soap bars in low concentrations. The structural formula of kojic acid is:



Databases searched for information on kojic acid in regard to Section II.A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopoeia/National Formulary (USP/NF).

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<sup>1</sup> Inclusion on the list of bulk drug substances that can be used in compounding under section 503A (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 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)).

1. *Stability of the API and likely dosage forms*

Kojic acid is a very reactive and unstable compound. It oxidizes easily in air, both as a solid or in aqueous solution. High temperature, exposure to light, and low pH can all substantially accelerate the decomposition process (Isaacs and Issacs 2013; Lee et al., 2002). Special sealing and formulation techniques are usually required to protect it from decomposing, but the preserving effects are limited. These factors can affect the stability of kojic acid when compounded into creams, gels, lotions, and solutions.

2. *Probable routes of API synthesis*

Kojic acid can be obtained from the fermentation of starches and sugars by a variety of microorganisms like *Aspergillus oryzae*. The fermentation process is usually aerobic (O'Neil 2006; Lewis 2007). Currently, chemical syntheses are not feasible for production of kojic acid.

3. *Likely impurities*

Likely impurities may include:

- Bioburden, such as residual molds or fungi
- Residual starting materials or reaction intermediates, such as oligosaccharides and sugar
- Degradation product(s) of kojic acid

4. *Toxicity of those likely impurities*

Residual microorganisms may be hazardous. Other impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section B.

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

Kojic acid is a colorless crystalline solid that is soluble in water. No information on the influence of particle size and polymorphism on bioavailability or product performance is 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*

Kojic acid is easily characterized with proton and Carbon-13 nuclear magnetic resonance (<sup>1</sup>H NMR and <sup>13</sup>C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), UV-Vis spectroscopy, and mass spectrometry (MS).

**Conclusions:** Kojic acid is a small organic molecule that is easily characterized with various analytical techniques. Preparation of kojic acid has been well developed. However, kojic acid is a very reactive and unstable substance, which can affect the stability of compounded products.

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

### *1. Nonclinical Assessment*

The following public database(s) were consulted in the preparation of this review: PubMed, TOXNET, EMBASE, Google/Google Scholar, and US Pharmacopeia (Searched using key words: kojic acid).

#### a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

Kojic acid is a chelation agent and an antioxidant. It is also a pigmentation inhibitor in plant and animal tissues and is used in foods and cosmetics to preserve or change the color of products. Kojic acid is used in dozens of cosmetics at concentrations from 0.1% to 4%. Kojic acid also has antibacterial and antifungal properties and is produced by many species of *Aspergillus* and *Penicillium*. Evidence suggests that kojic acid has protective effects against radiation-induced damage. The 30-day survival rate of mice pretreated with 300 mg/kg kojic acid subcutaneously 27 hours prior to a lethal dose (8 Gy, 153.52 cGy/min) of gamma irradiation was higher (60% vs 0%) than that of mice irradiated without pretreatment (Wang et al., 2014). Dogs pretreated with kojic acid before a lethal dose of 3 Gy of gamma irradiation had a 51-day survival rate of 66.7% compared to dogs not pretreated, which all died within 16 days post-irradiation (Wang et al., 2014).

#### b. Safety pharmacology

No information/data available.

#### c. Acute toxicity

The subcutaneous LD<sub>50</sub> of kojic acid in CFLP mice and CFY rats is 2.7 g/kg and 2.6 g/kg, respectively. Effects observed in mice at 4, 6.4, 10 and 16 g/kg included lethargy, injection site hemorrhage, ataxia, depressed respiratory rate and hunched posture. Effects observed in rats at 4, 6.4 and 10 g/kg included lethargy, piloerection, diuresis, and depressed respiration. The dermal and oral LD<sub>50</sub>s in Wistar rats are greater than 2 g/kg (Burnett et al., 2010).

#### d. Repeat dose toxicity

A 4-week dermal study in Wistar rats using doses of 0, 100, 300 and 1000 mg/kg/day revealed mildly decreased lymphocyte counts in male and female rats receiving 300 or 1000 mg/kg/day kojic acid. The no observed adverse effect level (NOAEL) of this study was determined to be 100 mg/kg/day (Burnett et al., 2010).

A 26-week toxicity study in SD rats at doses of 125, 250, 500 or 1000 mg/kg/day using oral gavage revealed increased liver enzyme activity in animals given 250, 500 or 1000 mg/kg/day. In high-dose (HD) animals, hematocrit and hemoglobin decreases were observed. At 500 and 1000 mg/kg/day, adrenal gland weights were increased. The NOAEL of this study was determined to be 125 mg/kg/day (Burnett et al., 2010).

A repeat-dose dermal toxicity study was conducted in black guinea pigs to evaluate depigmentation from kojic acid. Guinea pigs were dosed daily with 1% or 4% kojic acid (w/v) 6 days a week for 5 weeks. In comparison with vehicle-treated animals, no differences in pigmentation or morphology of the skin were observed (Tayama 2002).

Eye irritation potential was evaluated using a 3% (w/v) kojic acid solution in rabbits. No signs of irritation or inflammation were observed up to 72 hours post-dosing. A dermal irritation study in rabbits using 3% (w/v) kojic acid solution revealed no signs of skin irritation up to 72 hours post-dosing. The dermal sensitizing potential of kojic acid was evaluated in guinea pigs using topical applications of 30% (w/w) kojic acid solution. No effects were observed, and it was concluded that kojic acid was not a dermal sensitizer. Phototoxicity and photohypersensitization were evaluated in guinea pigs using 5% (w/v) kojic acid solution followed by UV exposure. No effects were observed (Burnett et al., 2010).

#### e. Genotoxicity

The mutagenic potential of kojic acid has been studied in several Ames tests using *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537, and *E. coli* strain WP2 uvrA with and without S9 metabolic activation. Kojic acid was found to be mutagenic in all strains at concentrations of 1000 µg/plate and above (Bjeldanes and Chew 1979; Wei et al., 1991; Ishikawa et al., 2006; and Burnett et al., 2010).

Kojic acid has been found to be clastogenic under certain conditions of evaluation (i.e., in Chinese Hamster Ovary cells at concentrations of 9 mg/mL and above (Burnett et al., 2010)).

Kojic acid was evaluated in an in vivo mouse micronucleus assay in NMRI mice that received single intraperitoneal doses of 187.5, 375, or 750 mg/kg. No genotoxicity was observed in this study. Kojic acid was considered not genotoxic in an in vivo Comet assay of liver, stomach, and colon cells from male Wistar rats that received two oral doses (21 hours apart) of 0, 1000 or 2000 mg/kg kojic acid (Burnett et al., 2010).

#### f. Developmental and reproductive toxicity

Effects on fertility and pregnancy were evaluated in SD rats using oral doses of 0, 25, 150 and 900 mg/kg/day. Males were treated daily for 9 weeks prior to mating and throughout mating. Females were treated for 2 weeks prior to mating through day 7 of gestation. Slightly delayed mating was observed in HD animals as well as decreases in mean litter size and number of implantations per litter (Burnett et al., 2010).

A study in pregnant NZW rabbits dosed from gestation day 6 through 18 with 0, 20, 100 or 500 mg/kg/day kojic acid revealed no change on litter size, post-implantation loss, litter and mean fetal weights, or embryonic and fetal development when compared to control animals (Burnett et al., 2010).

Female Wistar rats dosed from day 6 of gestation to day 17 of gestation with oral doses of kojic acid of 0, 100, 300 or 1000 mg/kg/day showed no signs of maternal toxicity or fetal developmental effects (Burnett et al., 2010).

#### g. Carcinogenicity

Dietary kojic acid was evaluated in p53-deficient mice fed 0, 1.5 and 3% (w/v) kojic acid for 26 weeks. Kojic acid caused diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells but no thyroid tumors. The incidence of altered hepatocellular foci was significantly increased at both concentrations of kojic acid in p53-deficient mice and at 3% in wild-type mice (Takizawa et al., 2003).

A second oral study was conducted in p53-deficient mice for 26 weeks with concentrations of 0.5%, 1% and 2% (w/v) kojic acid. Incidences of hepatocellular adenomas were dose-dependently increased in all groups (Burnett et al., 2010).

A 55-week study in Fisher 344 (F344) rats using oral doses of 0, 227 and 968 mg/kg/day was conducted. All HD-group animals had diffuse hepatocellular hypertrophy and/or vacuolization and formation of microgranulomas containing crystals and/or brown pigment; the incidence of the granulomas was significantly increased. Areas of placental glutathione S-transferase (GST-P)-positive foci were significantly increased in the liver of animals in the HD group. Incidences of hyaline casts and basophilic tubules were also significantly increased in the kidneys of the animals in the HD group. Diffuse follicular cell hyperplasia was noted in the thyroid glands in both groups of animals treated with kojic acid, and focal follicular cell hyperplasia, adenomas and/or carcinomas were observed in the HD-group animals. The HD group also had increased hypertrophy of cortical cells in zona fasciculata in the adrenal glands (Ota et al., 2009).

The carcinogenic potential of kojic acid was also evaluated by Higa et al., in 2007. In F344 rats, tumor initiation activity was evaluated in the liver. Possible weak initiation activity was detected. In an in vitro photo-reverse mutation assay, kojic acid induced chromosome aberration at 1.4 mg/mL concentration when combined with UV irradiation. In the absence of irradiation, no chromosome aberration was observed. In an in vivo photo-micronucleus study in mice using 1% or 3% (w/v) kojic acid-containing cream, no micronuclei were observed in mouse epidermal cells. The same authors evaluated a 3% (w/v) kojic acid-containing cream in a standard mouse skin carcinogenesis bioassay for tumor initiation and promotion activity. No skin nodules resulting from kojic acid carcinogenesis were observed.

A 78-week carcinogenicity study of kojic acid in mice has been conducted. Male and female B6C3F1 mice were fed diets containing 0%, 0.16%, 0.4%, or 1% (w/v) kojic acid. No kojic acid-specific effects were observed (Burnett et al., 2010).

#### h. Toxicokinetics

A 2001 pharmacokinetics study in rats evaluated oral, subcutaneous, and dermal exposure to kojic acid. Radiolabel from the single oral exposure (10  $\mu$ Ci/100 g) was found in the intestine within 3 hours and in the cecum within 6 hours post-dose. Distribution in tissues and organs was

very rapid, and maximum values were reached within 30 minutes post-dose. Very high levels of radiolabel were measured in the liver, kidneys, and pancreas, and high levels were measured in the lungs, heart, and spleen. In the blood, radioactivity was reported to be 20.63% and 25.05% of total administered radioactivity at 30 minutes and 1 hour, respectively, and decreased to background levels within 24 hours. The amount of  $^{14}\text{C}$  in the bile within 24 hours was approximately 0.5  $\mu\text{Ci}/10 \mu\text{Ci}$  administered dose. No radioactivity was detected in the bile samples from an enterohepatic circulation study (cannulated rats). Approximately 70% of the administered radioactivity was excreted in the urine within 48 hours, while excretion in the feces over the same time period was only 0.82% (Burnett et al., 2010).

Distribution in the tissues and organs following a single subcutaneous exposure to radiolabeled kojic acid (10  $\mu\text{Ci}/100 \text{ g}$ ) was slightly slower than that following the oral exposure. Distribution of radiolabel after a single dermal exposure to kojic acid (10  $\mu\text{Ci}/100 \text{ g}$ ) was even slower. High levels of radiolabel were measured in the kidney and liver 30 minutes and one hour after subcutaneous exposure, while no remarkable radioactivity was detected in the liver following dermal exposure. In the blood, radioactivity was reported to be 13.29% and 21.67% of total administered radioactivity at 30 minutes and 1 hour, respectively, following subcutaneous exposure and 5% of total administered radioactivity at 30 minutes following dermal exposure. The amount of  $^{14}\text{C}$  in the bile within 24 hours was approximately 0.76  $\mu\text{Ci}/10 \mu\text{Ci}$  and 0.5  $\mu\text{Ci}/10 \mu\text{Ci}$  for the subcutaneous exposure and dermal exposure, respectively. No radioactivity was measured in the bile samples from the enterohepatic circulation study (cannulated rats) after either exposure type. Approximately 50% and 56% of the subcutaneous and dermal administered radioactivity, respectively, was excreted in the urine within 48 hours. Excretion in the feces over the same time period was 2.62% and 1.58% of the administered subcutaneous and dermal doses, respectively (Burnett et al, 2010).

The major metabolites are glucuronide and sulfate conjugates of kojic acid. In pregnant rats, it has been demonstrated that kojic acid does pass to the fetus and can be excreted in the dam's milk when nursing (Burnett et al., 2010). The extent of systemic absorption that will occur after topical administration of kojic acid and how much of that systemically absorbed kojic acid would pass to the fetus or to the pups via the dam's milk is unknown. The overall risk associated with transfer of kojic acid to the fetus or to the pups from the dam's milk after topical administration is unknown, but it is anticipated to be minimal.

**Conclusions:** Nonclinical published data on topical use of kojic acid is limited. Kojic acid does not appear to be irritating to the skin or eyes (at up to 3%) and is not phototoxic (at up to 5%) in available animal studies. At concentrations up to 30%, kojic acid does not demonstrate skin sensitizing ability. The subcutaneous  $\text{LD}_{50}$  of kojic acid in CFLP mice and CFY rats is 2.7 g/kg and 2.6 g/kg, respectively. The dermal and oral  $\text{LD}_{50}$ s in Wistar rats are greater than 2 g/kg (Burnett et al., 2010).

A 4-week dermal study in Wistar rats using doses of 0, 100, 300 and 1000 mg/kg/day revealed mildly decreased lymphocyte counts in male and female rats receiving  $\geq 300$  mg/kg/day kojic acid. The NOAEL of this study was determined to be 100 mg/kg (Burnett et al., 2010). Kojic acid appears to be genotoxic as demonstrated by positive results in the Ames test and chromosomal aberration test. However, kojic acid does not appear to be genotoxic in an in vivo mouse micronucleus assay or an in vivo rat comet assay. Reproductive toxicity studies in rats demonstrated slight changes in fertility

parameters at 900 mg/kg (oral). Carcinogenicity studies are mixed in results, and the carcinogenic potential of kojic acid is unclear.

With limited dermal absorption shown in the in vitro human skin penetration study (see human pharmacokinetics section), the use of kojic acid in the compounding of dermal drugs may be reasonable from a pharmacology/toxicology perspective; however, nonclinical data suggest that its possible genotoxic potential and equivocal carcinogenicity data are of concern.

## 2. *Human Safety*

The following database(s) were consulted in the preparation of this review: PubMed, EMBASE, Web of Science, and the Cochrane Library.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for kojic acid through December 14, 2015. No cases were retrieved.

FDA's 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 associated with kojic acid through (December 30, 2015). No cases were retrieved.

There is significant under-reporting in any passive surveillance system, including FAERS and CAERS. Also, patients may not be aware that the adverse events they are experiencing may be related to their use of a particular substance, when the product name does not cover the name of the substance, or when the substance is among a large number of ingredients in the product.

In 2012 the European Commission's Scientific Committee on Consumer Safety re-evaluated the non-clinical and clinical data regarding the safety of kojic acid and stated the following: "Re-examination of the available data for Kojic Acid, used as a skin whitening agent at a concentration of 1.0% in leave-on creams, which are generally applied to the face and/or hands leads to the conclusion that it is safe for the consumers."

### a. Reported adverse reactions

Most of the published reports regarding therapeutic interventions with kojic acid for hyperpigmentation are related to the indication of melasma (Perez-Bernal et al., 2000).<sup>2</sup> Adverse event data from adequate and well-controlled trials evaluating kojic acid as a single active ingredient for the treatment of melasma are limited.

The following discussion describes some representative adverse event reports from clinical trials involving kojic acid alone or in combination with other active ingredients in the treatment of melasma.

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<sup>2</sup> Melasma is a type of hyperpigmentation. The majority of clinical studies of kojic acid use in hyperpigmentation identified in the search performed are in patients with melasma.

Lim (1999) conducted a 12-week, bilateral comparison trial enrolling 40 Chinese women with melasma who applied a gel containing kojic acid 2%, glycolic acid 10% and hydroquinone 2% to one side of the face and a gel containing glycolic acid 10% and hydroquinone 2% to the other side twice daily (split-face design). Subjects applied a physical sunscreen containing titanium dioxide over the study products. All subjects experienced redness, stinging, and mild exfoliation. The author reported that (s)ide effects experienced were “acceptable by most patients, and these disappeared by the first month.” The addition of kojic acid did not produce more irritation. Of three patients who dropped out of the study, the irritation was seen equally on both sides of the face, suggesting that this could be due to either the gel or the glycolic acid or hydroquinone or all three and not due to kojic acid alone.

Deo et al., (2013) conducted a 12-week, randomized, 4-arm trial with 67 women and 13 men with melasma in India, comparing the safety and efficacy of kojic acid 1% cream with 3 combination cream products containing kojic acid 1%: (i) kojic acid 1% and hydroquinone 2%; (ii) kojic acid 1% and betamethasone valerate 0.1%; and (iii) kojic acid 1%, hydroquinone 2%, and betamethasone valerate 0.1%. There were 3 subjects who experienced a “burning sensation” (one subject who applied kojic acid 1% cream and two subjects who applied kojic acid 1% and hydroquinone 2% cream). One subject who applied the cream containing kojic acid 1%, hydroquinone 2% and betamethasone valerate 0.1% developed “acneiform eruptions.”

Draelos et al., (2010) reported “no irritant or allergic contact dermatitis” among 80 subjects with mild to moderate facial dyschromia who were randomized to apply hydroquinone cream 4% or a combination product containing kojic acid, emblica extract and glycolic acid (formulation not otherwise described) twice daily for 12 weeks. The safety evaluation included adverse event reporting and an active assessment of burning/stinging, erythema, peeling and dryness. Although 10 subjects who applied the combination product reported stinging, none of them were withdrawn from the trial due to that symptom.

Garcia et al., (1996) treated 38 female and 1 male subjects for 3 months with a combination product containing kojic acid 2% and glycolic acid 5% gel applied to hyperpigmented patches on one side of the face and a combination product containing hydroquinone 2% and glycolic acid 5% gel applied to hyperpigmented patches on the other side of the face, starting with daily administration to be increased to twice daily. All subjects experienced burning and desquamation during the initial accommodation phase; no subjects discontinued treatment although some of them had to decrease the frequency of administration. The authors reported that the “kojic acid formulation was more irritating.”

The development of contact sensitization to kojic acid products is well documented in the literature. The following discusses representative case reports concerning this adverse event.

Nakagawa et al., (1995) conducted patch testing in 220 female patients for suspected cosmetic-related contact dermatitis. Five patients presented with facial dermatitis after exposure to products containing 1% kojic acid for 1 month to 1 year for the treatment of melasma. Patch testing confirmed allergic contact dermatitis with positive reactions to their own skin care products and to 5% kojic acid.

Serra-Baldrick et al., (1998) reported the development of allergic contact dermatitis in a 30-year-old-woman with post-inflammatory hyperpigmentation treated for 4 months with a combination cream product containing 3% kojic acid. Patch testing showed a positive reaction to the combination product and multiple concentrations of aqueous kojic acid (0.1%, 0.5%, 1%, and 5%).

Mata et al., (2005) reported that a 42-year-old woman developed an acute dermatitis on the face and neck after applying a product containing kojic acid to hyperpigmented patches for 3 days. Patch testing indicated positive reactions to her own product and various concentrations of kojic acid (0.5%, 1% and 3%). Previously, she had developed an eczematous eruption 2 months after using a product (not otherwise specified) to treat residual hyperpigmentation after sclerotherapy for varicose veins.

#### b. Clinical trials assessing safety

Most of the clinical trials involving kojic acid were designed to assess the comparative efficacy of combination products that included kojic acid in the treatment of melasma, although safety data collection could be among the study procedures in the clinical trials. Refer to Section II.B.2.a. above.

Burnett (2010) cited two unpublished human studies on repeat insult patch testing, one with a cream containing kojic acid 1% (54 subjects) and the other with a formulation (dosage form not specified) containing kojic acid 2% (218 subjects). In neither study was a sensitization response observed, although in the study with kojic acid 2%, irritancy was noted in the induction phase with four erythematous reactions.

In a long-term safety trial with follow up for about 14 years in 415 Japanese women treated with kojic acid for a variety of pigmentation disorders (melasma, solar lentigo, and pigmented cosmetic dermatitis), Yamamoto et al., (1998) identified no adverse systemic effects in the 78 women who had periodic evaluation with serum biochemistry and urine examination.

#### c. Pharmacokinetic data

There are no published reports of human pharmacokinetic (PK) studies following topical application of kojic acid *in vivo*. The European Commission's Scientific Committee on Consumer Products (SCCP) Opinion on Kojic Acid (European Commission, 2008) included a summary of an unpublished study on the systemic bioavailability of kojic acid. The study evaluated plasma concentrations of kojic acid following a single topical application of 500 mg of a cream containing 1% kojic acid to the entire surface of the facial skin (left and right cheeks) in six healthy postmenopausal Japanese women. Plasma concentrations of kojic acid were

measured before and 0.5, 1, 1.5, 3, 6, 12, and 24 hours after application. The European Commission report noted that “(k)ojic acid was detected in plasma of all patients at one or more blood collection times. Mean  $C_{max}$  was 1.54 ng/ml and the mean  $AUC_{0-24h}$  was 19.4 ng/ml x hr. Detection limit was 1 ng/ml.” This report indicates that kojic acid is absorbed following topical application.

In vitro application of a formulation containing 1% kojic acid at a dose of 2 mg/cm<sup>2</sup> for 16 hours to dermatomed skin from 4 donors (two samples per donor) using static diffusion cells showed that about 17% of the applied dose penetrated through the stratum corneum and was recovered in the epidermis and dermis ( $9.2 \pm 4.3\%$ ) and receptor fluid ( $7.8 \pm 6.8\%$ ). These data suggest that kojic acid can be absorbed following topical application (Nohynek et al., 2004).

Application of product with higher strength, larger amount or application area, or repeated dosing, as well as to diseased or non-intact skin, may lead to higher systemic exposure to kojic acid.

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

- Melasma

Fluocinolone acetonide, hydroquinone, and tretinoin cream, 0.01%/4%/0.05% (Tri-Luma) is an FDA-approved prescription drug indicated for the short-term treatment of moderate-to-severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

There are skin resurfacing laser devices cleared for the photocoagulation of pigmented lesions including melasma.

- Iron Chelation Uses

Wound Healing. There are many marketed medical products to promote wound healing. These can be categorized as devices, grafts, dressings, and drugs. Negative pressure wound therapy devices are cleared for marketing by FDA’s Center for Devices and Radiological Health (CDRH). A variety of graft materials (e.g., Apligraf and Dermagraft) are approved for treatment of diabetic ulcers. There are numerous combination product wound dressings cleared by CDRH. There is one biologic product approved to promote wound healing: Regranex gel. It has a warning regarding the potential increased risk of malignancy distant from the site of application. There is no information on comparative safety between kojic acid and the above products for wound healing.

Photodamage Prevention. There are prescription drug products approved for the mitigation of certain clinical signs of photodamage, but not for the prevention of photodamage (or for the treatment of photodamage itself). These products include tretinoin and tazarotene in cream formulations for topical use.

**Conclusions:** The available data suggest that the topical use of kojic acid may be associated with local irritancy (e.g., burning, stinging, and erythema). Generally, reported adverse reactions appeared to be transient and manageable with standard procedures. There have also been cases of allergic contact dermatitis documented in literature reports and confirmed with patch testing, but no reports of systemic adverse reactions.

Data regarding the safety of kojic acid as a single active agent in the treatment of hyperpigmentation disorders are limited. The data are confounded by the use of formulations with multiple active ingredients and poor trial designs without adequate controls. Most trials included sunscreen application as a concomitant procedure. Although the quality of available data is not ideal to evaluate systemic safety, because systemic exposure may be limited due to the limited surface area for application in the treatment of melasma, there does not appear to be a major safety concern associated with the use of kojic acid for this proposed use. Nonetheless, the safety data from clinical studies can only provide limited support for extrapolation to compounding because the systemic exposure of kojic acid from a compounded product cannot be reliably predicted due to its instability.

Regarding use in wound healing, the safety of the proposed concentrations up to 10% has never been studied in open wounds. There are no available data regarding the systemic exposure for this use, which may depend on many clinical variables including, but not limited to, the size of the wound and presence of infection. There are no safety data on kojic acid in prevention of photodamage.

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

The following database(s) were consulted in the preparation of this review:  
PubMed, EMBASE, Web of Science, and the Cochrane Library.

- 1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

- **Hyperpigmentation**

Information regarding the effectiveness of kojic acid in the treatment of hyperpigmentation disorders is limited. Most clinical trials involving kojic acid studied the treatment of melasma, and they present deficiencies in study design which make it difficult to assess efficacy. The following are representative reports of controlled trials providing evidence relating to the effects of kojic acid alone or in combination with other active ingredients in the treatment of melasma.

Lim (1999) evaluated 40 Chinese women with epidermal melasma in a double-blind, randomized, within-subject trial comparing a combination gel containing hydroquinone 2% and glycolic acid 10% with a combination gel containing kojic acid 2%, hydroquinone 2% and glycolic acid 10%. Subjects applied each gel twice daily to one side of the face for 12 weeks. Subjects used sunscreen with titanium dioxide SPF 15 daily.

The assessment of efficacy was based on clinical evaluation, photographs, and self-assessment questionnaires at weekly visits. The investigator graded improvement as 0–25%, 25–50%, 50–75%, > 75%, and clear, and scored these responses as +1 to +5, respectively. Although 45% of subjects

assessed the improvement as greater with the gel containing kojic acid, 7.5% assessed greater improvement with the gel not containing kojic acid and 47.5% assessed that there was no difference between the treatments. The difference in clearance of melasma was not statistically significant between treatments (2 out of 40 with the gel containing kojic acid and 0 out of 40 with the gel not containing kojic acid;  $p = 0.9$ ).

Deo et al., (2013) conducted a 12-week, randomized, single-blind (subjects blinded), parallel group trial enrolling 80 adults with melasma. The number of subjects with epidermal melasma (versus dermal or mixed melasma) in each treatment group varied. Subjects were randomized into four parallel groups:

- A – kojic acid 1% cream;
- B – kojic acid 1%, hydroquinone 2% cream;
- C – kojic acid 1%, betamethasone valerate 0.1% cream; and
- D – kojic acid 1%, hydroquinone 2%, betamethasone valerate 0.1% cream.

All subjects applied the study product nightly for 12 weeks and sunscreen with SPF15 during the day. Outcome measures included global assessments of response by physicians and subjects on 4-point scales and reduction in Melasma Area and Severity Index (MASI) scores from baseline to Week 12. The group that applied kojic acid 1% and hydroquinone 2% cream achieved the greatest mean percentage reduction in MASI score (71.87%), followed by the groups that applied kojic acid 1% cream alone (58.72%), kojic acid 1%, hydroquinone 2%, and betamethasone valerate 0.1% cream (54.23%) and kojic acid 1% and betamethasone valerate 0.1% cream (36.46%).

The design of this study lacks key treatment arms to demonstrate a contribution of kojic acid to the treatment effect. Without a placebo control, the background rate of improvement is unknown. In the absence of a treatment arm with hydroquinone 2% alone or betamethasone valerate 0.1% alone, the contribution of kojic acid cannot be evaluated. Moreover, responses to the triple combination and to the kojic acid 1% and betamethasone valerate 0.1% combination were lower than that to kojic acid alone, and these results are difficult to interpret. In addition, the article has not provided information on the rate of clearance of melasma in the study subjects.

Garcia et al., (1996) conducted a 12-week, randomized, active-controlled, bilateral comparison (split-face) trial in subjects with melasma. Thirty-eight female and 1 male subjects applied a combination product containing kojic acid 2% and glycolic acid 5% gel to one side of the face and another combination product containing hydroquinone 2% and glycolic acid 5% gel to the other side of the face twice daily for 3 months.

Outcome measures included clinical assessments (no scales provided), investigator evaluations of photographs using an ultraviolet light filter and subject impressions. The assessments of improvement from the investigator and subjects were compared with the photographs and an “overall percent reduction of pigment was calculated for the left and right face.” The results indicated that 51% of the subjects had an equal reduction in hyperpigmentation on both sides of the face; 21% had a greater reduction in hyperpigmentation on the hydroquinone side; and 28% had a greater reduction on the kojic acid side. The difference in pigment reduction between preparations containing kojic acid and hydroquinone was not significant ( $P > 0.05$ ). This study compared kojic

acid 2% against hydroquinone 2%, both in a gel formulation containing glycolic acid 5%. However, because hydroquinone 2% is not an approved treatment for melasma, such comparison does not establish the efficacy of kojic acid 2% unless it could be shown to be superior to hydroquinone 2%. In addition, the article has not provided information on clearance of melasma in the study subjects.

- Iron Chelation Uses

Wound Healing. No published reports of the clinical use of kojic acid for the purpose of promoting wound healing were found. The only available evidence with respect to use of kojic acid for wound healing is from a single report by Mohammadpour et al., (2013) of a nonclinical study of kojic acid in an in vivo wound model in Wistar rats. Although the authors claimed that kojic acid could accelerate wound healing, one of the major flaws in the design of this study is that the primary measurement was the percent mean wound healing at 8 days instead of evaluating either the time to complete wound closure or the incidence of complete wound closure at a specified time point. Complete wound closure is the most clinically relevant endpoint for evaluation in wound healing studies. Therefore, this study is not summarized in this review because it does not provide support for the clinical use of kojic acid for wound healing.

Photodamage Prevention. No published reports of the clinical use of kojic acid for the prevention of photodamage were found. One nomination cited a nonclinical reference on photodamage prevention in hairless mouse by kojic acid as an iron chelator (Mitani et al., 2001). The authors evaluated the anti-wrinkling activity of kojic acid by using hairless mice exposed to chronic solar-simulating ultraviolet (UV) irradiation, and claimed that at the end of a 20-week irradiation period, topical application of kojic acid before UV irradiation prevented wrinkling, epidermal hyperplasia, lower dermis fibrosis, and upper dermis increase of extracellular matrix components. The macroscopic wrinkling prevention effect was only presented in three photographs of the dorsal skin, and this effect remains to be confirmed in human studies.

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

Pigmentary disorders, including hyperpigmentation related to melasma, are not serious or life-threatening diseases or conditions.

Wound healing is a serious condition, and failure to adequately heal can result in permanent disability. Typical wound healing conditions in clinical practice include diabetic foot ulcers and decubitus ulcers.

Photodamage by itself is not a serious or life-threatening condition, although pathological changes predisposing to skin cancer may be associated with photodamage.

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

See Section II.B.2.d. above for approved therapies for melasma and wound healing as well as products for mitigation of clinical signs of photodamage that have been shown to be effective.

**Conclusions:** The majority of the trials evaluating the use of kojic acid in the treatment of melasma or hyperpigmentation disorders included combination products containing kojic acid compared with active controls. These combination products contained other topical therapies such as retinoids, hydroquinone, glycolic acid and botanical ingredients. All of the trials used adjunctive measures, such as sun protection with sunscreens and protective clothing.

Many of these trials showed improvement in the severity of melasma compared to baseline using kojic acid combination products either as a topical agent or with a peeling agent. However, the data are often confounded by the use of formulations with multiple active ingredients, inappropriate comparators, poor trial designs, incomplete descriptions of statistical methodology and variable outcome measures. The standard criterion of treatment success, clearance of melasma, is usually not presented in the reports. Thus far, there are insufficient quality data from clinical trials to assess whether kojic acid aids in the treatment of melasma or other disorders of dyspigmentation.

As well, the clinical data from such trials may only provide limited support for extrapolation to use in a compounding setting because of formulation differences, especially due to the instability of kojic acid, which may be aggravated by the presence of acidic peeling ingredients often used in combination in formulations directed at the proposed uses.

There is no published human clinical experience to support the use of kojic acid in wound healing or prevention of photodamage. There are only published nonclinical studies of kojic acid use in these conditions.

Approved products with established efficacy in the treatment of hyperpigmentation disorders, such as melasma and wound healing, are available. There are no products with established efficacy for the prevention of photodamage.

**D. Has the substance been used historically as a drug in compounding?**

Databases searched for information on kojic acid in regard to Section D of this consultation included PubMed, Martindale Extra Pharmacopeia (UK), European Pharmacopeia, Japanese Pharmacopeia, USP, Micromedex and WHO Global ICSR database.

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

Kojic acid has been used in combination with other drugs in pharmacy compounding in the United States for decades. For example, Garcia et al., (1996) conducted a study comparing the combination of kojic acid and glycolic acid to the combination of hydroquinone and glycolic acid for treatment of melasma in 1996. However, the extent to which kojic acid has been used in pharmacy compounding as a monotherapy for hyperpigmentation disorders or other uses is unknown.

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

Kojic acid is used primarily in combination with other substances for the treatment of melasma and other cutaneous disorders characterized by hyperpigmentation.

3. *How widespread its use has been*

The extent of use globally cannot be determined from available information. Kojic acid is widely used in Japan. Use has been reported in the United States, Canada, South America, India, South Korea, and other Asian countries.

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

Kojic acid was not found in the European, Japanese or British Pharmacopeias. However, cosmetics containing kojic acid are available in many countries. In Japan, kojic acid products are available and regulated as *quasi-drugs*, which are defined as “having a mild effect on the body but are intended for neither the diagnosis, prevention, nor treatment of disease, nor to affect the structure or function of the body” (Burnett et al., 2010).

**Conclusions:** Kojic acid is used primarily for the treatment of melasma and other disorders of hyperpigmentation. The substance has been used in pharmacy compounding in the United States and in other countries for decades, often in combination with other substances. The extent of use cannot be precisely determined, but its use has been reported in a number of countries in disparate parts of the world.

### III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate kojic acid for the 503A Bulks List. In the Agency’s view, after considering the information currently available to it, balancing the criteria *weighs against* kojic acid being placed on that list based on the following:

1. Kojic acid is well characterized in its physical and chemical properties. However, kojic acid is a very reactive and unstable substance, which can affect its content in compounded products, particularly if used in combination with acidic agents for depigmentation.
2. The available information regarding the safety of kojic acid for topical use in the treatment of disorders of hyperpigmentation indicates that reported adverse reactions are generally local, non-serious, and temporary, and consist primarily of local irritancy (e.g., burning, stinging and erythema), which is readily manageable, and allergic contact dermatitis. There have been no reports of systemic adverse reactions, and systemic exposure may be limited due to the limited surface area for application in the treatment of melasma. Nonetheless, the systemic exposure of kojic acid from a compounded product cannot be reliably predicted due to its instability. Furthermore, nonclinical data suggest possible genotoxic potential and equivocal carcinogenicity, which may be safety concerns for kojic acid. As well, melasma is a condition often occurring in pregnant women, and non-clinical studies have shown that kojic acid may pass to the fetus and can be excreted in breast milk.

There are no clinical data to support safety of kojic acid used as an iron chelating agent, either for wound healing or for prevention of photodamage.

3. There are some clinical data from a limited number of active controlled trials on the efficacy of kojic acid products in the treatment of melasma. However, the study designs, including the choice of controls and outcome measures, result in data that are generally inadequate to assess the contribution of kojic acid to efficacy. Support from these studies may be limited for a compounding setting due to the lack of assurance of stability of kojic acid in the compounded product. Alternative approved therapies for the treatment of hyperpigmentation disorders such as melasma are available.

There are no clinical data to support efficacy of kojic acid used as an iron chelating agent, either for wound healing or for prevention of photodamage.

4. Kojic acid has been compounded for use in the treatment of hyperpigmentation skin disorders such as melasma in the United States and other countries for decades, often in combination with other substances, although the extent of use cannot be precisely determined.

Based on the information the Agency has considered, a balancing of the four evaluation criteria weighs against kojic acid being added to the 503A Bulks List.

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Tab 4

Diindolylmethane

Tab 4a

## Diindolylmethane Nominations

# Fagron

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



<b>What is the name of the nominated substance?</b>	<b>Diindolymethane</b>
<b>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</b>	<p>Yes, Diindolymethane 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 Diindolymethane pharmacological actions are provided Garikapaty VP, Ashok BT, Tadi K, Mittelman A, Tiwari RK. 3,3'-Diindolymethane downregulates pro-survival pathway in hormone independent prostate cancer. <i>Biochem Biophys Res Commun.</i> 2006 Feb 10;340(2):718-25. Epub 2005 Dec 20. PubMed PMID: 16380095. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22280969">http://www.ncbi.nlm.nih.gov/pubmed/22280969</a></p> <p>Bhuiyan MM, Li Y, Banerjee S, Ahmed F, Wang Z, Ali S, Sarkar FH. Down-regulation of androgen receptor by 3,3'-diindolymethane contributes to inhibition of cell proliferation and induction of apoptosis in both hormone-sensitive LNCaP and insensitive C4-2B prostate cancer cells. <i>Cancer Res.</i> 2006 Oct 15;66(20):10064-72. PubMed PMID: 17047070. <a href="http://www.ncbi.nlm.nih.gov/pubmed/17047070">http://www.ncbi.nlm.nih.gov/pubmed/17047070</a></p> <p>Sarkar FH, Li Y. Indole-3-carbinol and prostate cancer. <i>J Nutr.</i> 2004 Dec;134(12 Suppl):3493S-3498S. Review. PubMed PMID: 15570059. <a href="http://www.ncbi.nlm.nih.gov/pubmed/15570059">http://www.ncbi.nlm.nih.gov/pubmed/15570059</a></p> <p>Li XJ, Park ES, Park MH, Kim SM. 3,3'-Diindolymethane suppresses the growth of gastric cancer cells via activation of the Hippo signaling pathway. <i>Oncol Rep.</i> 2013 Nov;30(5):2419-26. doi: 10.3892/or.2013.2717. Epub 2013 Sep 4. PubMed PMID: 24008339. <a href="http://www.ncbi.nlm.nih.gov/pubmed/24008339">http://www.ncbi.nlm.nih.gov/pubmed/24008339</a></p> <p>Kandala PK, Srivastava SK. Regulation of Janus-activated kinase-2 (JAK2) by diindolymethane in ovarian cancer in vitro and in vivo. <i>Drug Discov Ther.</i> 2012 Apr;6(2):94-101. PubMed PMID: 22622019. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22622019">http://www.ncbi.nlm.nih.gov/pubmed/22622019</a></p> <p>Kandala PK, Srivastava SK. Diindolymethane suppresses ovarian cancer growth and potentiates the effect of cisplatin in tumor mouse model by targeting signal transducer and activator of transcription 3 (STAT3). <i>BMC Med.</i> 2012 Jan 26;10:9. doi: 10.1186/1741-7015-10-9. PubMed PMID: 22280969; PubMed Central PMCID: PMC3298725. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22280969">http://www.ncbi.nlm.nih.gov/pubmed/22280969</a></p>
<b>Is the ingredient listed in any of the three sections of the Orange Book?</b>	The nominated substance was searched for in all three sections of the Orange Book located at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm</a> . The nominated substance does not appear in any section searches of the Orange Book.
<b>Were any monographs for the ingredient found in the USP or NF monographs?</b>	The nominated substance was searched for at <a href="http://www.uspnf.com">http://www.uspnf.com</a> . The nominated substance is not the subject of a USP or NF monograph.
<b>What is the chemical name of the substance?</b>	3,3'-methanediybis(1H-indole)
<b>What is the common name of the substance?</b>	3-(1H-Indol-3-ylmethyl)-1H-indole, DIM
<b>Does the substance have a UNII Code?</b>	SSZ9HQT61Z
<b>What is the chemical grade of the substance?</b>	no grade

<b>What is the strength, quality, stability, and purity of the ingredient?</b>	<p>Appearance: White or off-white crystalline powder  Melting Point: 165.0° - 169.0°C  Assay: ≥ 98.0%  Loss on Drying: ≤ 0.50%  Sulphated Ash: ≤ 0.10%  Lead: ≤ 2ppm  Arsenic: ≤ 2ppm  Benzene: ≤ 2ppm  Solvent: Ethanol  Total Plate Count: ≤ 500 cfu/g  Total Yeast &amp; Mold: ≤ 100 cfu/g  E. Coli: Negative  Salmonella: Negative  Pseudomonas: Negative  Staphylococcus Auerus: Negative  Melamine: Negative</p>
<b>How is the ingredient supplied?</b>	Powder
<b>Is the substance recognized in foreign pharmacopeias or registered in other countries?</b>	No foreign pharmacopeia monographs or registrations found.
<b>Has information been submitted about the substance to the USP for consideration of monograph development?</b>	No USP Monograph submission found.
<b>What dosage form(s) will be compounded using the bulk drug substance?</b>	Capsules
<b>What strength(s) will be compounded from the nominated substance?</b>	100mg
<b>What are the anticipated route(s) of administration of the compounded drug product(s)?</b>	Oral

<p><b>Are there safety and efficacy data on compounded drugs using the nominated substance?</b></p>	<p>Garikapaty VP, Ashok BT, Tadi K, Mittelman A, Tiwari RK. 3,3'-Diindolylmethane downregulates pro-survival pathway in hormone independent prostate cancer. <i>Biochem Biophys Res Commun.</i> 2006 Feb 10;340(2):718-25. Epub 2005 Dec 20. PubMed PMID: 16380095. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22280969">http://www.ncbi.nlm.nih.gov/pubmed/22280969</a></p> <p>Bhuiyan MM, Li Y, Banerjee S, Ahmed F, Wang Z, Ali S, Sarkar FH. Down-regulation of androgen receptor by 3,3'-diindolylmethane contributes to inhibition of cell proliferation and induction of apoptosis in both hormone-sensitive LNCaP and insensitive C4-2B prostate cancer cells. <i>Cancer Res.</i> 2006 Oct 15;66(20):10064-72. PubMed PMID: 17047070. <a href="http://www.ncbi.nlm.nih.gov/pubmed/17047070">http://www.ncbi.nlm.nih.gov/pubmed/17047070</a></p> <p>Sarkar FH, Li Y. Indole-3-carbinol and prostate cancer. <i>J Nutr.</i> 2004 Dec;134(12 Suppl):3493S-3498S. Review. PubMed PMID: 15570059. <a href="http://www.ncbi.nlm.nih.gov/pubmed/15570059">http://www.ncbi.nlm.nih.gov/pubmed/15570059</a></p> <p>Li XJ, Park ES, Park MH, Kim SM. 3,3'-Diindolylmethane suppresses the growth of gastric cancer cells via activation of the Hippo signaling pathway. <i>Oncol Rep.</i> 2013 Nov;30(5):2419-26. doi: 10.3892/or.2013.2717. Epub 2013 Sep 4. PubMed PMID: 24008339. <a href="http://www.ncbi.nlm.nih.gov/pubmed/24008339">http://www.ncbi.nlm.nih.gov/pubmed/24008339</a></p> <p>Kandala PK, Srivastava SK. Regulation of Janus-activated kinase-2 (JAK2) by diindolylmethane in ovarian cancer in vitro and in vivo. <i>Drug Discov Ther.</i> 2012 Apr;6(2):94-101. PubMed PMID: 22622019. <a href="http://www.ncbi.nlm.nih.gov/pubmed/22622019">http://www.ncbi.nlm.nih.gov/pubmed/22622019</a></p> <p>Kandala PK, Srivastava SK. Diindolylmethane suppresses ovarian cancer growth and potentiates the effect of cisplatin in tumor mouse model by targeting signal transducer and activator of transcription 3 (STAT3). <i>BMC Med.</i> 2012 Jan 26;10:9. doi: 10.1186/1741-7015-10-9. PubMed PMID: 22280969; PubMed Central PMCID: PMC3298725.</p>
<p><b>Has the bulk drug substance been used previously to compound drug</b></p>	<p>Capsules</p>
<p><b>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</b></p>	<p>Inhibits cell proliferation and induces apoptosis in certain types of Cancer</p>
<p><b>What is the reason for use of a compounded drug product rather than an FDA-approved product?</b></p>	<p>No FDA approved preparation for Diindolylmethane(DIM). DIM has found interest in many forms of Cancer. Its safe and no toxic effects make it safe to use when the toxicity of surrounding tissues is a concern. A study in Nasopharyngeal carcinoma(NPC), found DIM to induce apoptosis of infected cells and have preventive effects. (C. Chen, SM Chen, B. XU, Z. Chen, F. Wang, J. Ren, Y. XU, Y. Wang, BK Xiao, and ZZ Tao) (<i>In Vivo and in Vitro Study on the Role of 3,3'-Diindolylmethane in Treatment and Prevention of Nasopharyngeal Carcinoma Carcinogenesis</i> Aug;34(8):1815-21) Currently cervical dysplasia has only FDA approved surgical options. These options often lead to infertility. DIM has been shown in a pilot study to help treat dysplasia with no significant toxicity. (G. Del Priore, DK Gudipudi, N. Montemarano, A.M. Restivo, J. Malanoska-Stega, and A.A. Arslan(2010) <i>Oral Diindolylmethane(DIM):Pilot Evaluation of a Nonsurgical Treatment for Cervical Dysplasia Gynecol.Oncol.</i> Mar;116(3):464-7) DIM's non toxic and limited side effect profile make it an excellent candidate for continued use in a variety of preparations for physicians.</p>
<p><b>Is there any other relevant information?</b></p>	<p>All relevant information was expressed in the above questions</p>



## **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**

<b>Ingredient Name</b>	Diindolylmethane (3,3)
<b>Chemical/Common Name</b>	Diindolylmethane (DIM)
<b>Identifying Codes</b>	
<b>Chemical Grade</b>	Provided by FDA Registered Supplier/COA
<b>Description of Strength, Quality, Stability, and Purity</b>	Provided by FDA Registered Supplier/COA
<b>How Supplied</b>	Varies based upon compounding requirement
<b>Recognition in Formularies</b> <i>(including foreign recognition)</i>	Not Listed in USP/NF

### **Information on Compounded Bulk Drug Preparation**

<b>Dosage Form</b>	Varies based upon compounding requirement/prescription
<b>Strength</b>	Varies based upon compounding requirement/prescription
<b>Route of Administration</b>	Varies based upon compounding requirement/prescription
<b>Bibliography</b> <i>(where available)</i>	

**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.

Tab 4b

# FDA Review of Diindolylmethane



## DEPARTMENT OF HEALTH & HUMAN

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Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 29, 2016

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Director, Division of Prescription Drugs, Office of Unapproved Drugs and Labeling Compliance

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Diindolylmethane for Inclusion on the 503A Bulk Drug Substances List

### **I. INTRODUCTION**

Diindolylmethane (DIM) has been nominated in the form of oral capsules (100mg) for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Food, Drug, and Cosmetic Act (FD&C Act) for the treatment of cancer.

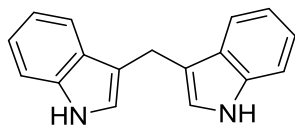
This substance is currently marketed as a dietary supplement as capsules (100 mg, 150 mg, 200 mg, 250 mg, and 300 mg), powder, and tablets (100 mg). DIM and its precursor, indole-3-carbinol (I3C), are sold and advertised as nutritional supplements purported to regulate sex hormone homeostasis.

We have reviewed 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 DIM 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).<sup>1</sup>

## II. EVALUATION CRITERIA

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

DIM is a small organic molecule, with the following molecular structure:



Databases searched for information on DIM for Section II.A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, and United States Pharmacopoeia/National Formulary (USP/NF).

#### 1. *Stability of the API and likely dosage forms*

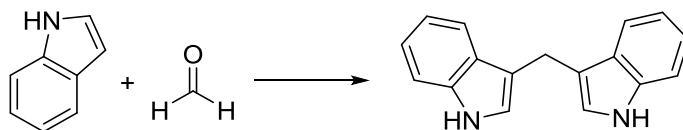
DIM is likely to be stable as a solid. In aqueous solution, it may be sensitive to UV light. In one study, about 80% degradation was found in the aqueous solution of DIM after 10 hours of exposure to UV light. Also, its stability in aqueous solutions is decreased at 37°C (Luo et al., 2013). When compounded as a solid, as is proposed in the nomination at issue here, DIM is likely to be stable when kept away from light at 4°C.

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<sup>1</sup> Inclusion on the list of bulk drug substances that can be used in compounding under section 503A (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 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)).

## 2. Probable routes of API synthesis

Currently, DIM can be obtained from the synthetic strategy shown below. Several studies have been carried out on varying the reaction conditions (e.g., acetic acid with water as the solvent) to optimize the yield, purity, and complicity of the processes (Hu et al., 2014; Kawamoto et al., 2012; Sun et al., 2013; Luo et al., 2013; Tayebie et al., 2013).



## 3. Likely impurities

Likely impurities may include residual starting materials, such as indole and formaldehyde; and trace amounts of solvents or reagents used in the reaction, such as Meldrum's acid (depending on different synthetic conditions).

Residual formaldehyde can be toxic to humans, but other impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section B.

## 4. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

DIM is a solid that is practically insoluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

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

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

**Conclusions:** DIM is a small organic molecule that is likely to be stable as a solid under ordinary storage conditions when kept away from light. The nominated substance is easily characterized with various analytical techniques, and the preparation of this compound has been well developed. The available information does not indicate concerns about the physical and chemical characterization of DIM or its use as a bulk drug substance for compounding under section 503A of the FD&C Act.

**B. Are there concerns about the safety of the substance for use in compounding? If so, are there approved therapies that may be as safe or safer?**

**1. Nonclinical Assessment**

The following public database(s) were consulted in the preparation of this review: PubMed and Google/Google Scholar.

- a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

DIM is an active metabolite of I3C, a phytochemical found in cruciferous vegetables (e.g. broccoli, cauliflower, kale, cabbage, Brussels sprouts, turnips, kohlrabi, bok choy, radishes, etc.) (Ciska et al., 2009). Published literature has shown that DIM inhibits the growth of human cancer cells of prostate, breast, colon, cervix, and pancreas origin, in vitro (Nachshon-Kedmi et al., 2004; Sarkar et al., 2004; Bhuiyan et al., 2006; Banerjee et al., 2011; Cho et al., 2011; Chen et al., 2011; Kandala et al., 2012a; Li et al., 2013; Kiselev et al., 2014). In vivo, DIM, alone or in combination with chemotherapeutic agents, was shown to have anti-tumor effects in mouse xenograft models of ovarian and prostate cancers (Kandala et al., 2012a; Kandala et al., 2012b). Published literature suggests that potential mechanisms of action of anti-tumor effects of DIM include cell growth inhibition; cell cycle arrest; inhibition of tumor cell migration; invasion, and metastasis; and activation of apoptosis (Garikapaty et al., 2006; Banerjee et al., 2011). In the presence of stomach acid, I3C dimerizes to the bioactive metabolite DIM (Aggarwal et al., 2005). Urinary DIM excretion may be a useful biomarker of I3C exposure (Fujioka et al., 2013).

- b. Safety pharmacology

No information available.

- c. Acute toxicity

No information available.

- d. Repeat dose toxicity

No information on repeat-dose toxicity studies conducted under good laboratory practices (GLP) was available in the public databases. In a proof of principle, non-GLP, in vivo pharmacology study of a mouse xenograft model of human prostate cancer, no significant adverse findings on body weights and select clinical pathology parameters of kidney and liver function were observed following administration of 2.5, 5, or 10 mg/kg [0.2, 0.4, or 0.8 mg/kg human equivalent dose (HED)] DIM by intraperitoneal injection, 3-times a week for 3 weeks (data not shown, Nachshon-Kedmi et al., 2004). In a non-GLP dietary feeding study in Sprague-Dawley rats, DIM induced expression of hepatic CYP1A1, CYP1A2, and CYP3A2 and decreased serum phosphorus level following administration

of 2 or 20 mg/kg (0.32 or 3.2 mg/kg HED) DIM for up to 12 months. No other significant adverse changes were noted in this study in food consumption, body weight gain, serum 25OH-D3 and testosterone levels, bone density, or histopathological findings (Leibelt et al., 2003). In six- or seven-day-old suckling C57BL/6 mice, administration of 20 – 100 mg/kg DIM once-daily for 3 days resulted in decreased immune cells in the spleen (e.g. F4/80<sup>+</sup>, CD11c<sup>+</sup>, CD19<sup>+</sup>, CD3<sup>+</sup> cells), induction of splenic white pulp atrophy, increased immune cell apoptosis, and decreased expression of various toll-like receptors (TLRs) in the spleen and intestine (Roh et al., 2011). In six- to eight-week-old C57BL/6 mice, administration of a single oral dose of 30 mg/kg DIM induced elevation of serum cytokines (e.g. IL-6, granulocyte colony-stimulating factor (G-CSF), IL-12, and IFN- $\gamma$ ) (Xue et al., 2008).

d. Mutagenicity

No information available.

e. Developmental and reproductive toxicity

No information available.

f. Carcinogenicity

No information available.

h. Toxicokinetics

No information available.

**Conclusions:** Based on data available in public databases, oral administration of DIM caused white pulp atrophy and decreased immune cell counts in the spleen of neonatal mice, and increased serum cytokines in adult mice. DIM induced hepatic CYP1A1, CYP1A2, and CYP3A2 in rats, suggesting drug-drug interactions may occur in patients. The available toxicology data indicate a potential safety concern. Both the potential safety concerns and the overall limited amount of available data raise concerns about the use of DIM in compounding under section 503A of the FD&C Act.

2. *Human Safety*

The following public database(s) were consulted using the search term Diindolylmethane in the preparation of this review: Pubmed, Google, and proceedings of the American Society of Clinical Oncology and the American Association for Cancer Research.

The Office of Surveillance and Epidemiology (OSE) conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for DIM through January 28, 2016. The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events for dietary supplements in the CFSAN Adverse Event

Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with DIM on February 4, 2016.

a. Reported adverse reactions

Most of the side effects of DIM reported to date have been limited to minor, reversible gastrointestinal symptoms. However, one group reported that concentrations of DIM achievable through diet exerted an unexpected proliferative effect on breast cancer cells (Marques et al., 2014). In addition, a case of central serous chorioretinopathy was reported in an otherwise healthy female who presented with headaches and blurry vision after 2-months of “excessive daily consumption” of DIM; visual improvement began 2 weeks after discontinuation of DIM and resolved to baseline after 8 weeks (Bussel et al., 2014).

The FAERS search yielded two cases of altered mental status with DIM use. The OSE review indicated that it could not assess a drug-event causal relationship because of the limited number of FAERS cases, insufficient data quality, and the presence of confounding medications.

The search of the CAERS database for adverse events yielded 18 reports (Table 1). Five reports were received of hepatotoxicity (including hepatitis, hepatocellular injury, liver function test abnormal), three reports of abdominal pain, and two reports of loss of consciousness. Several of these CAERS reports raise concern regarding potential safety signals, but these cannot be evaluated further given the lack of available data submitted with the cases.

**Table 1. CAERS Reports**

<b>Report No.</b>	<b>Age, Sex</b>	<b>Event(s) (Verbatim from report)</b>
73032	59 M	Nephritis, Blood creatinine increased, Eosinophilia, Pyuria
100680	82 Unk	Breast cancer, Breast mass
116734	42 M	Loss of consciousness, hemolytic anemia, autoimmune disorder
116934	61 F	Nausea, Hepatotoxicity, Hepatic enzyme increased, Malaise
123979	51	Abdominal pain, liver function test abnormal, alanine aminotransferase increased
114712	49 M	Nausea, Eating disorder symptom, asthenia, abasia, dysphagia, foaming at mouth
148312	52 F	Hypersensitivity, hepatocellular injury, vomiting, chills, tremor, body temperature increased
148560	21 M	Loss of consciousness, Pulse absent, Cardiac arrest Cardiomyopathy
154670	41 M	Carcinoid tumor, Vision blurred, Papilledema
169422	Unk	Pruritus, Urticaria, Throat tightness, Lip swelling, Swollen tongue
174571	56 M	Dyspnea, Fatigue, Respiratory tract congestion, Liver function test abnormal, Thrombosis
175701	23 M	Rectal hemorrhage, Abdominal pain upper, Hemorrhage, Colitis
177674	62 M	Muscular weakness, Vision blurred, Anger, Dehydration, Diabetes mellitus, Fatigue, Weight decreased, Aggression, Abasia, Hypersomnia
180951	55 F	Chest pain, Thrombosis, Pulmonary embolism, Lung injury

181166	57 F	Headache
183524	43 F	Nausea, Vomiting, Hepatitis, Hepatic enzyme increased
187178	Unk M	Blindness unilateral
191313	31 M	Abdominal pain, Chromaturia, Pain

b. Clinical trials assessing safety

Tables 2-5 summarize published literature describing the clinical experience to date with I3C and/or DIM. Published clinical studies contained no reports of serious toxicity; however, patient numbers were small, and it was unclear whether data on toxicity were systematically captured.

**Table 2. Clinical Experience with I3C and DIM in Healthy Volunteers**

<b>Author</b>	<b>Population</b>	<b>Treatment</b>	<b>Results</b>
Reed et al., 2006	Healthy female volunteers (n = 24)	I3C 400-1200 mg PO daily x 4 wk	<ul style="list-style-type: none"> <li>• I3C was undetectable in plasma.</li> <li>• Plasma C<sub>max</sub> of DIM rose following a single oral I3C dose of 1000 mg.</li> </ul> <p>The maximum tolerated dose (MTD) of I3C was 400 mg BID because of GI distress potentially related to the formulation, not I3C.</p>
Reed et al., 2008	Healthy volunteers (n = 24)	BioResponse formulation of DIM 50-300 mg PO single dose	<ul style="list-style-type: none"> <li>• Plasma C<sub>max</sub> of DIM rose following a single oral dose of 200 mg.</li> <li>• The MTD of DIM was 200 mg because of GI distress.</li> </ul>

**Table 3. Clinical Experience in Women with Abnormal Cervical Cytology**

Author	Population	Treatment	Results
Del Priore et al., 2010	Women with cervical intraepithelial neoplasia* (n = 64)	BioResponse formulation of DIM 2mg/kg daily vs. placebo x 3 mo	<ul style="list-style-type: none"> <li>No SAEs were reported</li> <li>No improvement in cervical cytology was demonstrated</li> </ul>
Bell et al., 2000	Women with cervical intraepithelial neoplasia*(n = 30)	I3C 200 or 400 mg/d vs. placebo x 12 wk	<ul style="list-style-type: none"> <li>I3C increased the urinary 2:16a-hydroxyestrone ratio, a physiologic change potentially associated with regression of CIN lesions.</li> <li>I3C induced regression of CIN</li> </ul>

\*Intraepithelial neoplasia is a precancerous condition.

**Table 4. Clinical Experience with I3C and DIM in Women at Risk for Breast Cancer**

Author	Population	Treatment	Results
Dalessandri et al., 20014	Postmenopausal women with history of early-stage breast cancer (n = 19)	BioResponse formulation of DIM 108 mg daily vs. placebo x 30 d	<ul style="list-style-type: none"> <li>DIM increased the 2-hydroxylation of estrogen urinary metabolites</li> </ul>
Kotsopoulos et al., 2014	Women with a BRCA1 mutation (n = 18)	BioResponse formulation of DIM 300 mg daily vs. placebo x 4-6 wk	<ul style="list-style-type: none"> <li>DIM increased BRCA1 mRNA expression</li> </ul>

**Table 5. Clinical Experience with I3C and DIM in Men with Prostate Disease**

Author	Population	Treatment	Results
Paltsev et al., 2014	Men with prostatic intraepithelial neoplasia (n = 14)	Infemin formulation of DIM 900 mg daily vs. placebo x 3 mo	<ul style="list-style-type: none"> <li>No SAEs were reported</li> </ul>
Heath et al., 2012	Men with early-stage prostate cancer (n = 36)	BioResponse formulation of DIM 225 mg PO BID x 14 days prior to prostatectomy	<ul style="list-style-type: none"> <li>No SAEs were reported</li> <li>DIM downregulated androgen receptor expression</li> </ul>
Gee et al., 2015	Men with early-stage prostate cancer (n = 45)	DIM 100 to 200 mg BID vs. placebo x 21-28 d prior to prostatectomy	<ul style="list-style-type: none"> <li>No SAEs reported</li> <li>DIM increased the urinary 2:16a-hydroxyestrone ratio</li> </ul>
Heath et al., 2010	Men with castrate-resistant, non-metastatic, PSA relapse prostate cancer (n = 12)	BioResponse formulation of DIM 75-300 mg BID	<ul style="list-style-type: none"> <li>No SAEs were reported</li> <li>Exposure dose proportional; steady state reached at 1 week</li> <li>MTD and RP2D: 225 mg BID</li> </ul>

c. Pharmacokinetic data

DIM in crystalline form is not absorbed when taken orally. Therefore, most published clinical studies to date were done with products formulated to improve oral bioavailability (e.g., BioResponse, Infemin).

The BioResponse formulation “encases small particles of DIM within a water-soluble matrix, containing  $\alpha$ -tocopherol polyethylene glycol succinate and phosphatidyl choline” to augment oral DIM bioavailability compared to the crystalline form of DIM as demonstrated in mice (Anderton et al., 2004) and humans (Jacobs et al., 2000). From a single oral dose of BioResponse at 100 mg and plasma measurements of DIM, the mean time to reach maximum concentration was 2.7 h; half-life was 3.7 h; maximum concentration was 32 ng/ml; and area under the curve was 136 h ng/ml (Reed et al., 2008). Plasma exposure to DIM appeared to be proportional to dose, from 50 mg up to approximately 200 – 300 mg. Consistent pharmacokinetic results for the BioResponse formulation were obtained in a subsequent study involving prostate cancer patients (Heath et al., 2010).

Infemin is a liquid formulation of DIM containing cod liver oil,  $\alpha$ -tocopherol acetate, and polysorbate 80 (Kiselev 2011). Although human safety and efficacy studies have been conducted to investigate the antitumor activity of DIM (Paltsev et al., 2014; Paltsev et al., 2016), no human pharmacokinetic studies using Infemin were identified.

The formulation of DIM used as an API in pharmacy compounding would be likely to have an impact on the oral bioavailability of a compounded product.

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

Numerous anticancer agents have been granted marketing approval by FDA after demonstration of safety and efficacy.

**Conclusions:** DIM and I3C have been studied clinically in a small number of patients. In general, gastrointestinal distress was dose limiting and no serious adverse events were reported. However, it is unclear whether data on toxicity were systematically captured in these studies, and a limited number of patients have been exposed in the clinical study setting. CAERS data suggest potential safety signals that were not identified in clinical studies. Overall, the safety profile of DIM has not been well characterized and there are potential signals for serious safety concerns.

**C. Are there concerns about whether a 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*

The results of clinical studies published to date show changes in biomarkers that the authors interpreted as evidence that DIM was absorbed and was biologically active.

However, no clinical publication to date describes an effect of DIM on any endpoint generally accepted in clinical oncology as being of clinical benefit or as being a surrogate for clinical benefit (tumor response, progression-free survival, etc.). See response to 2(b) above.

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

Cancer, a condition for which DIM is proposed, is a serious and life-threatening disease.

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

There are a number of FDA-approved drug products that have been established to be safe and effective for the treatment of cancer.

**Conclusions:** There is no clinical evidence to suggest that DIM administration would be efficacious in the prevention or treatment of cancer, a life-threatening disease for which there are numerous FDA-approved products. The efficacy data weigh against inclusion on the 503A bulks list.

**D. Has the substance been used historically as a drug in compounding?**

Databases searched for information on DIM in regard to Section D of this consultation included PubMed, clinicaltrials.gov, American Society of Clinical Oncology and the American Association for Cancer Research, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, USP/NF and Google.

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

FDA lacks information regarding whether DIM has been compounded as a drug.

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

An internet search using the search term diindolylmethane revealed that DIM is sold as a dietary supplement by pharmacies to “maintain” breast, cervical, and prostate cell health.

3. *How widespread its use has been*

We have no information regarding the extent of the use of DIM in compounded drug products. DIM is available as a dietary supplement in tablet and capsule form.

4. *Recognition of the substance in other countries or foreign pharmacopoeias*

A search of the British Pharmacopoeia (BP 2016), the European Pharmacopoeia (8<sup>th</sup> Edition, 2016, 8.8), and the Japanese Pharmacopoeia (16<sup>th</sup> Edition) did not show any listings for DIM.

**Conclusions:** Information is insufficient to determine the historical use of DIM in pharmacy compounding. Based on internet searches, it appears that DIM is sold at some compounding pharmacies as a prepackaged dietary supplement. We are not aware of official recognition of DIM as a drug by other countries.

### **III. RECOMMENDATION**

We have balanced the criteria described in section II above to evaluate DIM for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act. The substance was nominated for use in the treatment of cancer. In the Agency's view, after considering the information currently available, a balance of the criteria weighs *against* placing DIM on the 503A Bulks List.

1. DIM is well characterized in its physical and chemical properties.
2. There is, however, a relative lack of available nonclinical safety data, and the limited available data indicate potential safety concerns.
3. There also is a limited amount of clinical safety data. Although there are no reports of serious adverse events from that data, it is unclear whether data on toxicity were systematically captured. In addition, several CAERS reports raise concern regarding potential safety signals.
4. There is no clinical evidence to suggest that DIM administration would be efficacious in the prevention or treatment of cancer, a life-threatening disease for which there are numerous FDA-approved products.
5. There is insufficient information to evaluate the historical use of DIM in pharmacy compounding.

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Tab 5

Vasoactive Intestinal Peptide

Tab 5a

Vasoactive Intestinal Peptide  
Nomination

Hopkinton Drug   
compounding & wellness

52 Main St. Hopkinton, MA 01748 • phone:(508) 435-4441 • fax:(508) 435-5983

Hopkinton Drug, Inc.  
52 Main Street  
Hopkinton, MA 01748

2014 SEP -3 P 1:19

August 28, 2014

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

RE: Docket No. FDA-2013-N-1525

Dear Reviewer:

Hopkinton Drug, Inc. would like to nominate Vasoactive Intestinal Peptide to be included on the list of bulk drug substances that may be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act. Please see the attached supporting documentation.

Sincerely,



Jennifer Stevens  
Quality Control/Compliance Officer  
Hopkinton Drug, Inc.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Vasoactive intestinal peptide (acetate)
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	See item 1 of attachment B.
Is the ingredient listed in any of the three sections of the Orange Book?	no
Were any monographs for the ingredient found in the USP or NF monographs?	no
What is the chemical name of the substance?	C147H238N44O42S; His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH2
What is the common name of the substance?	Vasoactive intestinal peptide (human); vasoactive intestinal polypeptide; VIP
Does the substance have a UNII Code?	6J2WVD66KR
What is the chemical grade of the substance?	from synthetic
What is the strength, quality, stability, and purity of the ingredient?	greater than or equal to 95% in peptide purity (HPLC)
How is the ingredient supplied?	powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	no information available in foreign pharmacopeias

Has information been submitted about the substance to the USP for consideration of monograph development?	unknown
What dosage form(s) will be compounded using the bulk drug substance?	nasal spray
What strength(s) will be compounded from the nominated substance?	500mcg/ml
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).
Are there safety and efficacy data on compounded drugs using the nominated substance?	See attachments A and B.
Has the bulk drug substance been used previously to compound drug product(s)?	To my knowledge, the compounded version of VIP has always been a nasal spray. The nasal spray is stable for 132 days stored at refrigerated temperature (2-8°C); Stability is likely longer but the study was discontinued after 132 days. VIP was used as a nasal spray in the IRB-approved clinical trial (see Attachment 2 referenced in Attachment B) and has been used in that formulation since 2008.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	The drug is used as an intervention applied as part of a sequence of interventions for patients with chronic, systemic inflammatory response syndrome (CIRS); those with acquire pulmonary hypertension; or those with evidence of either grey matter atrophy or microscopic interstitial edema according to an IRB-approved protocol used to correct acquired pulmonary hypertension and CIRS.

<p>What is the reason for use of a compounded drug product rather than an FDA-approved product?</p>	<p>The FDA has not approved an IND for VIP. At one time Biogen-Idec listed clinical trials with Aviptadil, a trade name for VIP, on its website but a search performed 7/31/2014 showed no mention of VIP, vasoactive intestinal polypeptide or Aviptadil on the site. The basic reason to use VIP in patients with refractory symptoms and biochemical abnormalities is that it works and works safely. Efficacy is durable absent re-exposure. Before use of VIP, no drug, not even the successful protocol published by our group has been able to reverse the condition called CIRS-WDB. Dr. Ritchie Shoemaker (see Attachment B) has an IRB-approved retrospective clinical trial underway at this time to look at the genomics benefits of use of VIP using Next Generation DNA sequencing and RNA-sequencing. Dr. Shoemaker expects to have the data review begin in September 2014.</p>
<p>Is there any other relevant information?</p>	<p>See Attachment B.</p>
<p>Attachments</p>	<p>Please see the following attachments: Attachment A-bibliography on safety and efficacy data on VIP; Attachment B-letter from Dr. Ritchie Shoemaker addressing the FDA's request for 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) 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; and (4) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.</p>

Tab 5b

FDA Review of Vasoactive  
Intestinal Peptide



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993-0002

DATE: September 29, 2016

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THROUGH: Ramesh K. Sood, PhD  
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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of vasoactive intestinal peptide for inclusion on the 503A Bulk Drug Substances List

## I. INTRODUCTION

Vasoactive intestinal peptide (VIP) 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



### 1. *Stability of the API and likely dosage forms*

VIP is usually stable as a solid under normal storage conditions. However, its stability in aqueous solutions depends upon pH and storage temperatures. One study showed that degradation of VIP increased under basic conditions as pH increased from neutral to 13. At pH 13, VIP completely decomposed after 30 minutes at room temperature. However, under pH 2-7, no notable degradation was observed within 30 minutes (Cui et al., 2013). The stability of VIP also increased under lower temperatures. A dilute aqueous solution of VIP (12.5 µg/mL) showed 30% degradation under refrigerated storage conditions after 3 days. The higher concentrations, were found to be more stable under refrigerated storage with more than 85% contents remaining after 7 days. Frozen solutions of VIP at the investigated concentrations (12.5, 25.0 and 100 µg/mL) were found to be stable during the 7-day storage period (Cui et al., 2013).

### 2. *Probable routes of API synthesis*

VIP can be obtained from conventional solid-phase peptide synthesis, using 9-fluorenylmethoxycarbonyl (Fmoc) protecting group chemistry followed by cleavage of the peptide from the solid phase using trifluoroacetic acid (TFA) in the presence of 1,2-ethanedithiol (EDT) and water followed by purification by HPLC (Nicole et al., 2000).

### 3. *Likely impurities*

Likely impurities may include:

- Process related impurities, which are formed due to incomplete or side reactions during the manufacturing process:
  - Deletion sequences, which lack an amino acid due to incomplete coupling ( $n - 1$ , where  $n$  refers to the intended number of amino acids in the peptide sequence)
  - Insertion sequences formed by addition of two of the same amino acids in one step ( $n + 1$ )
  - Diastereomers formed when amino acid(s) epimerize, usually during removal of side chain protecting groups
  - Modifications of functional groups like asparagine and glutamine, which are susceptible to deamidation
- Residual solvents and reagents used in the reaction, cleavage, and purification processes. Solvents used in the early portion of the synthesis include dimethylformamide (DMF). TFA is used as the main reagent of the cleavage reaction. Acetonitrile is typically used as solvent in HPLC purification steps.
- Smaller peptide fragments from degradation of VIP

### 4. *Toxicity of those likely impurities*

The synthesis process for VIP should be carried out to limit potential residual solvents, DMF, TFA, and acetonitrile. Acceptable limits on the residual amounts of these substances should be set and maintained.

Immunologic toxicity may occur due to:

- Peptide related impurities and degradants

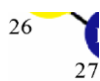
- Aggregate formation
- Unknown effects of leachables from the nasal spray container on the structural integrity of the VIP peptide

Toxicity of impurities is further discussed in section B.

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

VIP is a solid and is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

VIP has been analyzed by circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopy, showing it to have a helical conformation with an  $\alpha$ -helix (residues 11- 26) and 2  $\beta$ -bends (residues 2-5 and 1-10) at the N-terminus. The N-terminal and C-terminal domains are believed to be important for bio-activity and receptor recognition. The secondary structure of VIP is shown below (Igarashi et al., 2011).



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

VIP can be characterized by high-performance liquid chromatography (HPLC) and mass spectrometry (MS). Due to the known secondary structure of VIP, analytical evaluation by an appropriate bioassay would confirm the consistency of proper secondary structure of VIP.

The nomination proposed to deliver compounded VIP via a nasal spray. Local and systemic exposure to VIP, determining both safety and efficacy, will be dependent in large part on the delivery of VIP from the nasal spray device. The accurate and consistent administration of an API via a nasal spray depends upon multiple factors (e.g., dimensional controls of the spray device for reliable delivery of intended volume, consistent drop size distribution, plume geometry, spray pattern, and priming requirements for device).

**Conclusions:** VIP is a peptide hormone prepared by solid-phase peptide synthesis. The 28 amino acid peptide has been shown to exhibit secondary structure such as  $\alpha$ -helix and  $\beta$ -bends, and an appropriate bioassay may be useful to confirm the proper secondary structure of the formulated VIP. The stability of aqueous solution depends upon pH and storage temperature. Very dilute solutions also are prone to degradation and potential aggregate formation, which may increase the potential immunogenicity of the peptide API. The usability period of the compounded product for nasal spray will depend upon maintaining proper solution pH and storage temperature of the solution. Delivery of VIP will be dependent on the complex factors associated with a nasal spray device.

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

### *1. Nonclinical Assessment*

The following public database(s) were consulted in the preparation of this portion of this review: Embase, PharmaPendium, PubMed, TOXNET and Web of Science.

#### a. Pharmacology of the drug substance and its likely impurities

As stated above, VIP is a 28-amino acid neuropeptide, which is a member of the secretin superfamily of peptide hormones. Although VIP was originally found in the small intestine (Said and Mutt 1970), VIP has been detected endogenously throughout the body and is considered a major regulatory peptide in the mammalian brain. VIP is produced by a variety of cell types, in addition to those found in the central and peripheral nervous systems. Other cells that synthesize VIP are some types of endocrine and immune cells. Consistent with being widespread, VIP exerts pleiotropic functions by acting as a neurotransmitter or immunomodulator in organs such as the brain, heart, lung, pancreas, thyroid, genitourinary tract, and the immune system (Smalley et al., 2009; Wu et al., 2011; Morell et al., 2012; Sanlioglu et al., 2012).

VIP binds to three different G protein-coupled receptors (GPCRs) on the surface of cells to mediate its physiological effects, namely VPAC<sub>1</sub>, VPAC<sub>2</sub>, and PAC<sub>1</sub>, each of which show differential tissue expression (Laburthe et al., 2007; Onoue et al., 2008). Of note, VIP is 68%

similar in amino acid structure to the pituitary adenylate cyclase-activating peptide (PACAP), a peptide hormone. VIP and PACAP bind to the receptors VPAC<sub>1</sub> and VPAC<sub>2</sub> with similar affinities (Onoue et al., 2008), and the downstream molecular signaling events triggered by ligand binding to its receptors have been well characterized (Dickson and Finlayson 2009).

Diverse physiological roles of VIP have been identified, including its role as a potent vasodilator and bronchodilator (Said and Mutt 1970; Palmer et al., 1986a), coordination of circadian rhythms in the brain (Aton et al., 2005), stimulation of insulin secretion (Schebalin et al., 1977), and regulation of pro- and anti-inflammatory factor production (Chorny et al., 2005; Kulka et al., 2008). Due to its wide array of biological actions, VIP has been investigated for its therapeutic potential to treat a number of diseases such as asthma, arthritis, diabetes, and neurodegeneration (Delgado et al., 2001; Wu et al., 2011; Morell et al., 2012; Sanlioglu et al., 2012). Under normal conditions, VIP is present in the circulation at low levels (in serum, mean: approximately 42 pg/ml, normal range: 12.9 – 98.5 pg/ml) (Hejna et al., 2001; Petkov et al., 2003). Circulating VIP is thought to originate from perivascular VIP-producing nerve fibers (Henning and Sawmiller, 2001). Certain conditions, such as prolonged exercise (Hilsted et al., 1980), extended fasting (Øktedalen et al., 1983), or gastrointestinal tumors (Hejna et al., 2001), have been associated with elevated levels of circulating VIP. Although it is detected in blood, local VIP in tissues is primarily responsible for its biological effects.

#### b. Pharmacokinetic data

In a conscious dog model (n=5) where porcine VIP was infused at 2.8 pmol/kg/min for 40 min, the half-life, metabolic clearance rate, and distribution volume were calculated as follows: 1.80±0.1 minutes, 39.3±5.2 ml/kg/min, and 103.7±14.8 ml/kg, respectively, indicating high clearance of the injected VIP substance (Chayvialle et al., 1981). A comparison between portal vein infusion and systemic infusion detected a higher plasma level of VIP obtained via the systemic infusion (maximum detected level 81.0±10.1 pmol/l) compared to direct portal infusion delivery (maximum detected level 25.6±3.4 pmol/l). The estimated loss of VIP upon hepatic transit was 72.9±2.1%, indicating that VIP is quickly broken down in the liver. After the infusion was stopped, the plasma VIP concentration decreased to baseline in 14 minutes after systemic administration, compared to 8 minutes after portal infusion, indicating a higher clearance via the hepatic pathway.

Consistent with the Chayvialle data described above, PK data reported in conscious dogs (IV) and anesthetized pigs (intraportal injection) showed a similar pattern of rapid hepatic clearance for VIP in both species (Mitchell et al., 1982).

Hassan et al., (1993) confirmed the high clearance rate of VIP shown by the Chayvialle study above. Additionally, Hassan et al., administered VIP via intravenous injection, which showed that the radioactively labeled VIP was taken up and accumulated in the lungs in the first minute of delivery. Within 15 minutes of delivery, the radioactivity was cleared from the lungs and redistributed into the kidneys, gastric mucosa, liver, and small intestine.

When injected intravenously, VIP was found to cross the blood brain barrier (BBB) by a nonsaturable transport system, without enzymatic degradation and in amounts likely to affect

brain function. VIP transport through the BBB seems to be unidirectional and VIP tends to stay in the central nervous system (CNS), rather than being cleared into the blood (Dogrukol-Ak et al., 2003).

Using a quantitative radioactivity assay, VIP was detected in rat brain extracts as an intact molecule when delivered via the intranasal route, but not via the intravenous route. Furthermore, radioactivity levels of VIP were found to be higher following intranasal exposure compared to intravenous exposure (Dufes et al., 2003).

Due to its short systemic half-life and its quick metabolism, various techniques have been employed to extend VIP's systemic residence time as an intact molecule, including enveloping VIP molecules in micelles or in a polymer-based nanocarrier (Reichstetter et al., 2013). Under the conditions of a study by Reichstetter et al., (2013), it was found that both encapsulation delivery techniques were able to prolong the longevity of VIP compared to unformulated VIP preparations. The authors concluded that this delivery method could increase systemic exposure of VIP when used as a treatment option in the clinical setting.

To improve the efficiency of VIP by protecting it from the degrading milieu in the nasal cavity, Gao et al., (2007) incorporated VIP into nanoparticles (NP) where they were able to entrap it into NP with a high efficiency. The effects of the VIP formulations on the learning impairment of rats was tested using the Morris water maze task<sup>2</sup> showed that intranasal administration of VIP-NP improved the spatial memory in a dose-dependent manner. Animals treated with 12.5µg/kg VIP loaded by the unmodified nanoparticles did not show significant improvement compared to their control counterparts. In contrast, animals injected with 25µg/kg VIP-NP presented considerable improvement. When VIP was processed using the wheat germ agglutinin (WGA) modification method, a dose of 12.5µg/kg produced significant improvement in learning and memory in the water maze task. In addition, acetylcholinesterase activity, an enzyme that was measured in rat hippocampus at the termination of the behavioral experiments showed an increase in cholinergic activity in rats injected with VIP-WGA that was similar to levels detected in sham control animals.

### c. Safety of substance impurities or degradants

The synthesis process described above identified three solvent related impurities (DMF, TFA and acetonitrile). Levels of these solvents should be limited as part of the API manufacturing process. In addition, the potential for occurrence of impurities related to protein sequencing errors and degradation of the peptide should be minimized. Toxicity of these substances will be discussed in the clinical safety section.

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<sup>2</sup> The water maze task is widely used as a behavioral test to measure spatial learning and memory. It can be a very accurate study of learning, memory, and spatial working and can also assess damage to cortical regions of the brain. This behavioral assay measures the escape latency of animals from the water by learning to reach the platform in a given time period. Exposure to certain drugs that damage the brain results in a delay of the time that the animal reaches the platform.

d. Acute toxicity<sup>3</sup>

No acute toxicity data were found for VIP.

e. Repeat dose toxicity<sup>4</sup>

VIP was administered either subcutaneously (SC, 40µg/ml) or intranasally (IN, 40µg/ml or 200µg/ml; volume of solution used in this study was not indicated) in a mouse model (number of animals was not specified) for 7 consecutive days. The mice were injected daily for a week with the peptide  $\alpha\beta_{25-35}$  to model Alzheimer's disease (Cui et al., 2012). Although a VIP solution containing a dose of 40µg/ml (SC & IN) did not show improvement in spatial learning or memory performance, an improvement was seen among mice treated with 200 µg/ml VIP/IN. An important conclusion from this study was the finding that intranasal administration of VIP can lead to detectable levels in the brain in mice. Unfortunately, this study is of limited value in terms of the toxicological assessment because it was not designed to capture essential endpoints usually evaluated in traditional repeat dose toxicity studies, like body weights, organ pathology and histopathological evaluation.

In a another mouse model, VIP was delivered via subcutaneous injection using either micelles or a polymer-based nanocarrier formulation for a period of 4 or 8 weeks where mice (5 animals/dose) were treated 3 times weekly with either 62.5µg/kg or 300 µg/kg dose of VIP (Reichstetter et al., 2013). Toxicity endpoints included evaluation of body weights, clinical chemistry and cardiotoxicity (e.g., cardiac troponin, myosin light chain, slow twitch troponin) endpoints, and observation of the injection site. Under the conditions of the study, both techniques were able to prolong the longevity of VIP compared to unformulated VIP preparations. Toxicity endpoints measured showed no significant differences in mice injected with either VIP or vehicle control (saline). Similar to the study cited above for Cui et al., (2012), this study lacks a more comprehensive toxicological assessment.

f. Genotoxicity<sup>6</sup>

No genotoxicity data were found for VIP.

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<sup>3</sup> *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.

<sup>4</sup> A *repeat dose toxicity study* refers to an in vivo animal study that seeks to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histopathology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

<sup>5</sup>  $\alpha\beta_{25-35}$  is the active peptide of the neurotoxic  $\alpha\beta$  peptide, which is linked to deficits in learning and memory loss and is detected at high levels in patients with neurodegenerative diseases. Animal models enriched with  $\alpha\beta$  peptide are used to study neurodegenerative diseases such as Alzheimer's.

<sup>6</sup> The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and of 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.

g. Developmental and reproductive toxicity<sup>7</sup>

No developmental or reproductive toxicity data were found for VIP.

h. Carcinogenicity<sup>8</sup>

A number of assays have been conducted to evaluate the carcinogenicity potential of VIP. However, none of the studies reported in the literature is considered a standard carcinogenicity study as described per the International Conference of Harmonisation (ICH) protocols.<sup>9</sup> In one case, the effect of VIP either alone or in conjunction with a colon tumor promotor, azoxymethane (AOM), on the development of colon cancer was tested in a rat model (Tatsuta et al., 1995). Wistar rats (n=25/group) were treated by subacute injection of AOM (7.4 mg/kg body weight in saline solution) once weekly for 10 weeks along with subacute injection of VIP (suspension in olive oil at 20 µg/kg body weight) every other day for 45 weeks. Another group of rats, which served as a control group, was administered an ornithine decarboxylase (ODC) inhibitor, 1,3-diaminopropane (DAP)<sup>10</sup> (2.5 g/L in water), thought to decrease the rate of colon cancer caused by VIP. Co-administration of DAP and VIP significantly reduced the enhanced colon carcinogenesis caused by VIP alone. Other non-standard studies on the carcinogenic potential of VIP were found in the literature but none of the studies was designed to study the carcinogenic potential of VIP (Iishi et al., 1987; Iishi et al., 1992; Fernandez-Martinez et al., 2010).

No intranasal carcinogenicity data were found in the literature for VIP.

i. Toxicokinetics<sup>11</sup>

No toxicokinetic data were found for VIP.

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<sup>7</sup> Reproduction toxicity studies are usually designed to assess the human gender and age groups that will be exposed to the proposed substance. Developmental toxicity refers to adverse effects that are seen 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.

<sup>8</sup> 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.

<sup>9</sup> Guideline for Industry The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals March 1996, which can be found on this link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074911.pdf>

<sup>10</sup> ODC was found to be the rate limiting enzyme in the formation of polyamines in a human colon carcinoma cell line. Polyamines are considered key factors in cell growth regulation. The idea is that ODC is needed for expression of VIP increase in colon carcinogenesis; therefore, the authors postulate that when ODC is inhibited, a decrease in VIP takes place leading to a decrease in colon cancer.

<sup>11</sup> Toxicokinetics (TK) is the field of study where the relationship between the systemic exposure of a substance in experimental animals and the level of toxicity in exposed animals is evaluated. In the context of drug development, TK calculation is used to establish the relationship between systemic exposures in toxicology experiments in animals and the corresponding exposures in humans.

**Conclusions:** VIP is a small peptide that can be found endogenously. It has been associated with a number of physiological activities. It has a short half-life and quick metabolism via hepatic clearance. VIP is capable of crossing the blood brain barrier. Nonclinical data found in the literature are of limited value and cannot be relied on to characterize the toxicity potential of VIP due to the absence of data for chronic toxicity, genotoxicity, carcinogenicity or reproductive/developmental toxicity testing. No data were found that characterize the effect of long-term intranasal exposure to VIP.

## 2. *Human Safety*

The following databases were consulted in the preparation of the clinical portion of the review: PubMed, Embase and Web of Science.

- Bioavailability/pharmacokinetics

The bioavailability and pharmacokinetics (PK) of VIP are significant determinants of potential safety and efficacy. Published data on the PK for intravenous infusion of VIP do not provide comprehensive analyses, such as distribution and bioavailability. Domschke et al., (1978) reported the results for intravenous infusion of purified porcine VIP at doses of 0.6, 1.3, 3.3 pmol/kg/min over 30 minute periods (n = 4). Compared to baseline ( $3 \pm 2$  pmol/L), circulating VIP in plasma rose to high plateau levels for the higher doses ( $154 \pm 22$ ,  $351 \pm 12$  pmol/L). After infusion was discontinued, plasma VIP concentrations fell rapidly with a half-life of approximately 1 minute. For infusion rates of 1.3 and 3.3 pmol/kg/min, the volume of distribution was 14 and 13 ml/kg, respectively, and the metabolic clearance rate was 8.6 and 9.5 ml/kg/min, respectively.

Holm-Bentzen et al., (1981) also performed pharmacokinetic analyses, but with a background intravenous infusion of pentagastrin (100 ng/kg/h) (n = 6). The authors were interested in studying the effect of VIP on gastric acid secretion and used pentagastrin to elevate gastric acid secretion to a submaximal level, likely to expand the detection range of acid output. The mean plasma VIP concentration before infusion was  $5.5 \pm 0.2$  pmol/L. With increasing intravenous infusion doses of 0.3, 0.9 and 2.7  $\mu$ g/kg/h, the steady state plasma VIP concentration increased to 28, 106, and 336 pmol/L, respectively. Elimination of VIP was rapid with half-life of 2 and 21 minutes, which was described as two exponential functions, or bi-exponential.

Gill et al., (1990) used a similar approach to Domschke et al., (1978) (n = 6). Using an intravenous infusion rate of 3.9 pmol/min/kg for VIP, the results were as follows: steady state level was 56 pmol/L, half-life was 0.8 min, clearance rate was 69.6 ml/min/kg, and apparent volume distribution was 125 ml/kg.

Data regarding PK following nasal administration are described in the Efficacy: CIRS section below.

- API Impurities

As described above, the synthesis of VIP can result in the formation of incorrectly coded peptides and VIP degradation can result in peptide fragments. VIP, peptide impurities, and peptide degradation products can each be responsible for generating immunologic responses. Such variation in the synthesis

process can precipitate clinical consequences. The general basis for safety concerns related to substances comprised of amino acids are described in an FDA guidance that discusses these concerns in the context of therapeutic protein products.<sup>12</sup> (Both the identity and purity of the API factor significantly into the safety and efficacy of VIP compounded formulations. Additional discussion of the occurrence of immunogenicity reactions is addressed in the Safety: Published clinical trials section.)

a. Reported adverse reactions

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events and found no reports.

FDA's Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events for dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with VIP and found no reports. It is important to note that there is significant under reporting in any passive surveillance system, including FAERS and CAERS. Also, patients may not be aware that the adverse events they are experiencing may be related to their use of a particular substance, when the product name does not cover the name of the substance, or when the substance is among a large number of ingredients in the product. Also, the lack of adverse event reports may be a reflection of limited compounding of the substance.

b. Clinical trials assessing safety

A summary of the published clinical trials and safety trials involving healthy subjects that reported VIP administration is included in the Appendix. Trials of a product containing aviptadil (synthetic VIP) and phentolamine for treatment of erectile dysfunction have been excluded as there is no way to discern the relationship of an adverse reaction specifically to VIP. Trials of radiolabeled VIP for the purpose of medical imaging were also excluded. Safety outcomes are listed in the summary table. In general, the reactions to orally inhaled or injectable VIP were mild and consistent with VIP's known vasodilatory activity. Galie et al., (2012), studying VIP (aviptadil) use to treat pulmonary arterial hypertension, reported that a "group of patients" within the investigator group's multicenter trial of orally inhaled VIP had an increase of VIP plasma auto-antibodies (which was severe in two cases). It cannot be ascertained based on the publically available information what specific substance(s) may have initiated these immunologic reactions, such as VIP or miscoded/fragmented peptide impurities in the VIP synthesis. However, it can be concluded that there is documentation of such reactions and the possibility of additional severe immunologic reactions associated with VIP cannot be ruled out.

c. The availability of alternative approved therapies that may be as safe or safer

There are no products approved in the United States for the treatment of the condition described as CIRS.

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<sup>12</sup> Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, available online at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm338856.pdf>.

**Conclusions:** Although the majority of adverse events associated with VIP appear to be relatively mild and attributable to VIP's vasoactive properties, VIP has been associated with severe immunologic reactions. As noted in Section II.A, without sufficient chemistry controls on the production of VIP, synthesis is likely to result in other peptides of shorter and longer amino acid length, as well as peptides with incorrect amino acid sequencing, in any product compounded. This raises significant safety concerns with regard to the potential for the development of immunological reactions.

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

The following databases were consulted in the preparation of the clinical portion of the review: PubMed, Embase and Web of Science.

- Mechanism of action for nominated use

As previously described, VIP is a 28-amino acid chain neuropeptide found in the central nervous system and throughout the human body, and it has been investigated as a potential pharmacologic treatment for a wide variety of conditions. The specific mechanism by which VIP has been postulated to treat the nominated use, a condition described as chronic inflammatory response syndrome (CIRS), is to correct a humoral deficiency of VIP postulated to have been detected in 98% of CIRS patients (Shoemaker et al., 2013).

- Nasal spray administration

The nominated use of VIP is for intranasal administration. As discussed above, the nasal spray device with which a drug is applied to the nasal mucosa can make a substantial difference in bioavailability (Djupesland 2013). In addition, nasal drug delivery can be affected by numerous physiologic factors such as low membrane permeability depending on the size of the molecule, rapid clearance from the nasal cavity due to mucociliary clearance, and, particularly for peptides such as VIP, enzymatic degradation (Campbell 2012). These factors should be considered in determining the suitability of VIP administration via compounded nasal formulations.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

The use for which VIP has been nominated, CIRS, is the subject of research. CIRS is not listed in the 2015 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), a medical classification list by the World Health Organization (taken from <http://www.icd10data.com/> on August 21, 2016). Furthermore, CIRS is not listed in the Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0 March 2016, taken from <http://www.meddra.org/> on August 21, 2016).

The term *CIRS* was found to have been used in three publications, and the effects of VIP are assessed only in the earliest of these publications (Shoemaker et al., 2013; Shoemaker et al., 2014; Ryan et al., 2015). Twenty individuals identified by the investigator as having CIRS-Water Damaged Building

(CIRS-WDB), a condition in which CIRS is proposed to be attributable to exposure to water-damaged buildings, were enrolled in the VIP trial.<sup>13</sup> In addition, entry criteria included a rise in pulmonary artery systolic pressure in exercise that exceeded 8 mmHg. These patients were reported to have failed prior treatments for CIRS-WDB, such as changes in their environment and treatment with various exogenously administered substances to “correct” plasma levels of 12 endogenous chemicals, including VIP. No additional entry criteria were specified, such as reported symptoms or plasma levels of various substances subsequently measured during the study. No primary endpoints or efficacy thresholds were stated.

The study design appears to have intended that subjects self-administer 50 mcg of aviptadil (synthetic VIP) via nasal inhalation, 4 times a day for 18 months. Eight patients were reported to have consistently used VIP “three or four times a day,” 4 patients used VIP “once or twice a day,” 3 patients used VIP “before strenuous activity only,” and 5 patients stopped using VIP at various points during the trial. For the latter 5 subjects, only data collected while using VIP was subject to statistical analysis. A total of 10 substances were serially measured in the plasma at baseline before any treatment for CIRS-WDB, at a timepoint “AC2” following administration of all treatments for CIRS-WDB except VIP, and two additional time points, after 12 and 18 months of VIP administration, respectively.<sup>14</sup> Timepoint AC2 was a mean of 36 months following baseline. No information is provided regarding the comparison of study subjects and controls at timepoint AC2. No statistical analyses were presented regarding the study outcomes at 12 months. At 18 months, mean VIP and MSH levels were reported to be significantly lower than the control means. No statistically significant differences were found between mean levels of the other 8 substances measured and control means.

Shoemaker et al., (2013) measured VIP levels (presumably in blood, although not specifically stated in the publication) for VIP delivered via intranasal administration. The mean VIP level of normal control subjects was 28.9 pg/ml. The mean VIP for the 20 study subjects enrolled in the trial was 9.3 pg/ml at baseline, prior to receiving any therapeutic intervention for CIRS-WDB. After failing treatments for CIRS-WDB, at timepoint AC2, the subjects’ mean VIP level was 14.4 pg/ml. VIP levels were 12.3 and 16.6 pg/ml at 12 and 18 months of VIP treatment, respectively. These measurements were not described as having been taken in a specified relationship to dosing. Shoemaker et al., report that the levels of VIP increased in VIP treated subjects after timepoint AC2, but did not reach the level of the normal control subjects.

No additional published reports of clinical pharmacokinetic studies for intranasal administration of VIP were identified.

The single, open label clinical trial of VIP in CIRS, specifically CIRS-WDB, fails to establish the efficacy of VIP, or that there is systemic exposure from intranasal administration of VIP, due to substantial limitations in the study design. The study population is inadequately defined, with apparent

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<sup>13</sup> These patients were “confirmed to be exposed to WDB by observation of illness acquisition solely following water intrusion followed by the presence of either (1) visible microbial growth; (2) speciation of molds by QPCR DNA testing; or (3) musty smells.”

<sup>14</sup> Substances measured in plasma included VIP, melanocyte stimulating hormone (MSH), complement C4a, transforming growth factor beta-1, vascular endothelial growth factor, matrix metalloproteinase 9, estradiol, testosterone, vitamin D, and lipase.

lack of documentation regarding mold exposure and specification of requisite signs and symptoms of CIRS. The evidentiary standard on which VIP's effect was to be determined was not pre-specified nor systematically explained in relationship to the results.

Additional information regarding the condition that the nominator describes as CIRS, including a stepwise treatment protocol for "mold illness," can be found at <http://www.survivingmold.com/> (retrieved August 21, 2016.) No additional supportive data regarding the use of VIP in CIRS appears on the site.

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

CIRS is not listed in either ICD-10 or MEDRA as a recognized disease and there is insufficient literature regarding the medical consequences of CIRS to make this determination.

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

There are no products approved in the United States for the treatment of the condition described as CIRS.

**Conclusions:** The condition for which VIP has been nominated, CIRS, is not listed in either ICD-10 or MEDRA. The use of VIP in an apparent subtype of CIRS, CIRS-WDB, has been described in a single published trial, which fails to clearly establish benefits of VIP administration.

#### **D. Has the substance been used historically as a drug in compounding?**

Databases searched for information on VIP in regard to Section II.D of this consultation included PubMed, clinicaltrials.gov, Natural Medicines Database, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, USP/NF and Google.

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

VIP was first isolated from porcine small intestine in 1970 (Said et al., 1970). There is insufficient information available to determine how long VIP has been used in pharmacy compounding.

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

Results from a Google search using the terms *vasoactive intestinal peptide compounding pharmacy* indicate that VIP is/has been compounded in both nasal and injectable forms. Based on internet searches, it appears that compounding pharmacies have been preparing VIP as a nasal spray for the treatment of CIRS as part of the Shoemaker Protocol (Shoemaker et al., 2013). In addition, at least one pharmacy has been using VIP as an ingredient in injectable erectile dysfunction products.

3. *How widespread its use has been*

Insufficient data are available from which to draw conclusions about the extent of use of VIP in compounded drug products.

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

Aviptadil (synthetic VIP) has been approved in New Zealand, Denmark, and the United Kingdom in combination with phentolamine for intracavernosal injection for the symptomatic treatment of erectile dysfunction in adult men.

A search of the British Pharmacopoeia (BP 2016), the European Pharmacopoeia (8<sup>th</sup> Edition, 2016, 8.8), and the Japanese Pharmacopoeia (16<sup>th</sup> Edition) did not show any listings for VIP or aviptadil.

**Conclusions:** Information is insufficient to determine the historical use of VIP in pharmacy compounding. Based on internet searches, it appears that compounding pharmacies have been preparing VIP as a nasal spray for the treatment of CIRS.

### III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate vasoactive intestinal peptide for the 503A Bulks List. In the Agency's view, after considering the information currently available to it, a balancing of the criteria *weighs against* vasoactive intestinal peptide being placed on that list based on the following:

1. This 28-amino acid peptide has been shown to exhibit secondary structure such as  $\alpha$ -helix and  $\beta$ -bends and an appropriate bioassay may be useful to confirm the proper secondary structure of the formulated VIP. The stability of aqueous solution depends on pH and storage temperature. Very dilute solutions also are prone to degradation and potential aggregate formation, which may increase the potential immunogenicity of the peptide API.
2. Nonclinical data found in the literature are inadequate to characterize the toxicity potential of VIP, particularly for use in a potentially chronic condition. Although clinical data suggest that most clinical adverse effects due to VIP are mild and can be attributed to its vasoactive properties, severe immunologic adverse effects have been reported. It is well documented that such events can be associated with miscoded peptides or peptide fragments that can form during synthesis of peptide APIs such as VIP.
3. We have reviewed available data on the effectiveness of this substance and found that there is inadequate clinical information regarding the nominated use for the condition described as CIRS. The single trial of the use of VIP to treat the condition described as CIRS-WDB does not provide a basis to conclude that VIP is associated with improvement in the proposed clinical features described as CIRS. Neither nonclinical nor clinical data establish that intranasal delivery of VIP results in systemic exposure.

4. Information is insufficient to determine the historical use of VIP in pharmacy compounding, but VIP is currently compounded in the United States, including for use as a nasal spray in the treatment of CIRS.

Based on the information, described above, a balancing of the four evaluation criteria weighs against VIP being added to the 503A Bulks List.

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## Appendix: Vasoactive Intestinal Peptide Clinical Studies - Evaluation of Safety

Title/Author	Exposed to VIP	VIP Dosing	Physiologic Responses and Adverse Events
<b>Studies of Pulmonary Effects</b>			
Vasoactive intestinal peptide causes bronchodilatation and protects against histamine-induced bronchoconstriction in asthmatic subjects. Morice et al., (1983)	N=7 Patients with atopic asthma	IV infusion of VIP (6 pmol/kg/min) for 15 min	Bronchodilation in all subjects.  Tachycardia and cutaneous flushing during infusion. Three subjects said they felt hot and three described the sensation as throbbing, None found the infusion uncomfortable.
The effect of inhaled vasoactive intestinal peptide on bronchial reactivity to histamine in humans. Barnes PJ, Dixon CM (1984)	N=6 Mild asthma and known bronchial hyperresponsiveness to inhaled histamine	Orally inhaled VIP (100 µg)	No significant effect on baseline airway function; no change in heart rate or blood pressure. Significant protective from histamine-induced bronchoconstriction.  It was reported that no subjects experienced any adverse effects after inhalation.
Vasoactive intestinal peptide as a bronchodilator in severe asthma Morice AH, Sever PS (1986)	N=16  Study 1: 8 Study 2: 8  Recovering from severe acute asthma	Both studies: all subjects received orally inhaled salbutamol, some received prednisolone and theophylline Study 1: i.v. infusion of placebo for 15 min, VIP (6 pmol/kg/min) for 30 min, placebo for 15 min, salbutamol 5 mcg/min for 30 min Study 2: i.v. infusion of placebo for 15 min, VIP (6 pmol/kg/min) for 30 min	Both studies: bronchodilation, increase in peak expiratory flow rate, tachycardia  No additional safety data were reported.
A comparison of the ventilatory, cardiovascular and metabolic effects of salbutamol, aminophylline and vasoactive intestinal peptide in normal subjects Morice et al. (1986)	N=2  Healthy adults	IV infusion of placebo followed by VIP (6 pmol/kg/min) for 30 min	Increase in pulse rate, plasma catecholamines, and packed cell volume.  No additional safety data were reported.
Effect of infused vasoactive intestinal peptide on airway function in normal	N=6 Non-asthmatic males	1,3,6 pmol/kg/min IV Vasoactive Intestinal Peptide (VIP) infused over 15 min	Facial flushing, hypotension, tachycardia were dose limiting effects.

subjects Palmer et al., (1986b)			
Effect of vasoactive intestinal peptide (VIP) on propranolol-induced bronchostriction Crimi et al., (1988)	N=6 Asthmatic patients	70 ug VIP saline solution prepared in 0.9% saline with albumin (2.5 mb/ml) aerosolized by a nebulizer and administered by 30 tidal breaths	It was reported that there were no adverse events.
Ventilatory effects of substance P, vasoactive intestinal peptide, and nitroprusside in humans Maxwell et al., (1990)	N=6 Healthy adult males	IV infusions on separate days in randomized order: placebo, nitroprusside, substance P, VIP (1, 3, and 6 pmol/kg/min)	Increase in heart rate but lack of significant ventilatory change with VIP.  No additional safety data were reported.
Bronchodilation by an inhaled VPAC(2) receptor agonist in patients with stable asthma Lindén et al., (2003)	N=24 Patients with moderate stable asthma	Ro 25-1553 (a VIP analogue) 100 micrograms or 600 micrograms via oral inhalation	Rapid bronchodilatory effect within 3 min of VIP administration which diminished within 5 hrs after inhalation, but was evident for 12 hours after inhalation.  It was reported that there were no adverse events.

<b>Studies of Cardiovascular Effects</b>			
Effects of indomethacin and ( $\pm$ )-propranolol on the cardiovascular and renin responses to vasoactive intestinal polypeptide (VIP) infusion in man. Unwin et al., (1987)	N=12 2 groups of 6 healthy males	IV infusion of VIP (6 pmol/kg/min)	Following VIP, cutaneous flushing, increased heart rate and plasma renin activity were observed, and decreased forearm vascular resistance.  No additional safety data were reported.
Peptide histidine valine: its haemodynamic actions and pharmacokinetics in man differ from those of vasoactive intestinal peptide and peptide histidine methionine Gill et al., (1990)	N=6 Healthy adults	IV infusion (pmol/min/kg): peptide histidine valine (PHV) (2.75), peptide histidine methionine (PHM) (2.91), VIP (3.9)	VIP infusion followed by increased heart rate; decreased diastolic but not systolic blood pressure; and increase in forearm blood flow. Painless flushing of the infused limb in 3 subjects.  No additional safety data were reported.
<b>Studies of Cutaneous Effects</b>			
Cutaneous responses to vasoactive intestinal polypeptide in chronic idiopathic urticaria Smith et al., (1992)	N=20 10 controls, 10 patients with chronic	Sequential intradermal injections at 2 min intervals of compound 48/80, substance P, neurokinin A, calcitonin	Significant increase in mean wheal area for all concentrations of VIP, but not in flare or cutaneous blood flow, compared to controls

	idiopathic urticaria	gene-related peptide, and VIP (0.5, 1.0, 2.0 $\mu\text{mol/L}$ )	No additional safety data were reported.
Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal polypeptide Gherardini et al., (1998)	N=33 Patients with venous stasis ulcers	Comparison of iontophoresis of calcitonin gene-related peptide and VIP with placebo transdermal iontophoresis (saline).	No safety data were reported.
Cutaneous reactions and sensations after intracutaneous injection of VIP & acetylcholine in atopic eczema (AE) patients and healthy controls Rukweid R, Heyer G (1998)	N=14 Healthy subjects & N = 14 AE patients	VIP was dosed alone at $1.5 \times 10^{-7}$ , $1.5 \times 10^{-6}$ and $1.5 \times 10^{-5}$ M into the volar forearm of subjects	VIP induced wheal and flare and dose dependent pruritis as well as increased blood flow as measured with laser Doppler flowmetry.  No additional safety data were reported.
Administration of acetylcholine & VIP to atopic eczema (AE) patients Rukweid R, Heyer G (1999)	N=28 14 healthy subjects & 14 AE patients	VIP $1.5 \times 10^{-5}$ M & Ach (0.55M) were injected (10 microl) intra- cutaneously into the volar forearm.	Erythema and itching surrounding injection site.  No additional safety data were reported.
Evidence for a role for VIP in active vasodilatation in the cutaneous vasculature of humans Bennett et al., (2003)	Study 1: N=8 healthy (6 males; 2 females) Study 2: N=7 healthy (4 males; 3 females)	VIP(10-28) was dosed at 54 microM, 107 microM, or 214 microM by perfused via intradermal microdialysis at 2 microl min <sup>-1</sup> for approximately 1 hr. VIP (7.5 microM) was then added to the perfusate containing VIP(10-28) for 45-60 min. Individuals then underwent 45-60 min of whole-body heating.	All VIP(10-28)-treated sites displayed an attenuated dilatation in response to the VIP (a dose-dependent reaction). VIP(10-28) attenuated the increase in cutaneous vascular conductance during heat stress.  No additional safety data were reported.
Mechanisms of VIP-mediated vasodilation in human skin Wilkins et al., (2004)	N=43 Healthy subjects (19 women & 24 men)	Infusions were administered to skin sites via intradermal microdialysis. Study 1: VIP doses ranged from 25 to 800 pmol Study 2: 200pmol VIP with H1 or H2 receptor antagonist	VIP-mediated vasodilation involves nitric oxide-dependent component at doses above 100 pmol.  No additional safety data were reported.
Vasoactive intestinal peptide fragment VIP <sub>10-28</sub> and active vasodilation in human skin Wilkins et al., (2005)	Four studies were included: Study 1 (n = 12) Study 2 (n = 6) Study 3 (n = 6) Study 4 (n = 6)	Red blood cell flux was measured using laser Doppler flowmetry; cutaneous vascular conductance (flux/mean arterial pressure) normalized to maximal vasodilation	VIP <sub>10</sub> augmented vasodilation compared to exogenous VIP  No additional safety data were reported.

Peripheral amplification of sweating – a role for calcitonin gene-related peptide Schlereth et al., (2006)	N = 6 Healthy subjects	Infusion via dermal microdialysis. When administered alone, VIP was used at $10^{-5}$ and $10^{-6}$ M. VIP $10^{-5}$ , $10^{-6}$ , $10^{-7}$ and $10^{-8}$ M with ACh	VIP had no significant effect on axon reflex sweating. ACh-induced skin blood flow was unaltered by VIP.  No additional safety data were reported.
Cutaneous nociception and neurogenic inflammation evoked by PACAP38 and VIP Schytz (2010a)	N=16 Healthy volunteers	Intradermal injections of 200 pmol PACAP38, 200 pmol VIP and placebo into the volar forearm	VIP induced a significantly larger increase in skin blood flow, flare and wheal than PACAP38. Mild short-lasting cutaneous pain was similar between treatments.  No additional safety data were reported.
<b>Studies of Headache/Migraine</b>			
Vasoactive intestinal polypeptide evokes only a minimal headache in healthy volunteers Hansen et al., (2006)	N=12 Healthy adults	VIP (8 pmol/kg per min) or placebo (0.9% saline) was infused for 25 min	Flushing, palpitation, heat sensation and headache
Vasoactive intestinal peptide causes marked cephalic vasodilation, but does not induce migraine Rahmann et al., (2007)	N=12 Migraine without aura	8 pmol kg <sup>-1</sup> min <sup>-1</sup> VIP or placebo	Headache, palpitation, heat sensation, flushing
Investigation of carbachol and PACAP38 in a human model of migraine Schytz HW (2010b)	N = 12 Healthy volunteers	Intradermal injection of 200 pmol VIP.	VIP induced cutaneous pain, central sensitization (assessed by area of punctuate hyperalgesia around the injection site), neurogenic inflammation and mast cell degranulation.
Investigation of the pathophysiological mechanisms of migraine attacks induced by pituitary adenylate cyclase-activating polypeptide-38 (PACAP38). Amin et al., (2014)	N=22 Females, migraine without aura	IV infusion for 20 min of either PACAP38 (10 pmol/kg/min) or VIP (8 pmol/kg/min)	VIP subjects (4 pts., 18%) reported lower incidence of migraine compared to PACAP38 (16 pts; 73%).  VIP patients reported flushing (21), heat sensation (22), palpitation (21), nausea (6), photophobia (6), phonophobia (4), shivering (8), dizziness (3), feeling of numbness in both arms (2), tingling in chest (2), vomiting (1), feeling of tightening all over the body (1), visual disturbances (1), tingling in a finger (1)
<b>Studies of Endocrine Effects</b>			
Vasoactive intestinal polypeptide stimulation of	N = 6 male	VIP infusion of 65 pmol per min for 90 minutes	VIP infusion increased heart rate, hematocrit, plasma renin activity in

prolactin release and renin activity in normal man and patients with hyperprolactinaemia: effects of pretreatment with bromocriptine and dexamethasone Lightman et al., (1984)	volunteers , N = 7 hyperprolactinemics	(total dose 5.8 nmol)	normals and patients. Prolactin was increased in normal only.  No additional safety data were reported.
Paradoxical response of growth hormone to peptide histidine methionine in acromegaly: comparison with the effects of thyrotropin-releasing hormone and vasoactive intestinal peptide Watanobe et al., (1991)	N=8 Active acromegaly	IV bolus injection: thyrotropin-releasing hormone (TRH) (500 µg), VIP (100 µg), or peptide histidine methionine (PHM) (100 µg).	It was reported that no serious side effects were observed.
Effects of intravenously infused pituitary adenylate cyclase-activating polypeptide on adenophyophyseal hormone secretin in normal men. Chiodera et al., (1996)	N = 7 Normal male subjects	VIP infusion of 4 pmol per kg per min for 60 min	During VIP infusion, serum prolactin and heart rate increased, but blood pressure decreased.  Flushing of modest intensity was reported in all subjects.
A suppressive effect of dexamethasone (DEX) on adrenocorticotropin (ACTH) response to vasoactive intestinal peptide (VIP) in Cushing's disease: a parallel modulation by DEX of ACTH responses to VIP and corticotropin-releasing hormone. Watanobe H, Tamura T (1997)	N=7 Patients with Cushing's disease	4 IV loads: (1) corticotropin-releasing hormone (CRH) (100 µg), (2) VIP (100 µg), (3) CRH (100 µg) 60 min after i.v. bolus injection of 1.0 mg dexamethasone, (4) VIP (100 µg) 60 min after an IV bolus injection of the same dose of DEX	It was reported that no serious side effects were observed.
Oxytocin enhances the prolactin response to VIP in healthy women Chiodera et al., (1998)	N=7 Healthy women; on the 22nd day of two consecutive normal menstrual cycles.	VIP (4 pmol · kg <sup>-1</sup> · min <sup>-1</sup> in 50 mL saline) infused IV for 60 minutes; either the presence or absence of oxytocin (2 IU injected & 0.07 IU/min infused for 60 minutes).	The infusion of VIP decreased blood pressure (mean arterial pressure at time 0 of the VIP test: 92.0 ± 1.2 mm Hg; at time 60: 79.4 ± 1.3 mm Hg) and increased heart rate (time 0: 71.2 ± 3.3 beats/min; time 60: 90.6 ± 4.2 beats/min). Similar values were observed during the VIP plus oxytocin test. Flushing (modest) was the common side effect observed in all subjects during the tests.  It was reported that no behavioral or other side effects were observed.
<b>Studies of Other Effects</b>			
Somastatin does not block the effect of vasoactive intestinal peptide on bile secretion in man	N = 10 Patients with complete	Highly purified porcine VIP infused at a dose of 1.33 mcg per kg per hr	VIP infusion increased bile secretion by acting at the ductular level.

Nyberg et al., (1992)	biliary fistulas		No additional safety data were reported.
Inhaled Vasoactive Intestinal Peptide Exerts Immunoregulatory Effects in Sarcoidosis Prasse et al., (2010)	N=20 Sarcoidosis and active disease	50 mg synthetic VIP (Aviptadil; Bachem, Basel, Switzerland) four times daily by inhalation by way of an ultrasonic nebulizer (Optineb; Nebu-Tec, Elsenfeld, Germany) for 28 days.	Dry throat, hoarseness, syncope, cough, and hemoptysis, increased creatinine, flatulence and diarrhea were reported.

## Tab 6

# Drug Products That Present Demonstrable Difficulties for Compounding: Background and Proposed Evaluation Criteria



## **Drug Products That Present Demonstrable Difficulties for Compounding: Background and Proposed Evaluation Criteria**

### **I. Background**

Section 503A of the Food, Drug, and Cosmetic Act (21 U.S.C. 353a) (FD&C Act or the Act) generally governs the application of federal law to pharmacy compounding. Under section 503A of the Act, compounded drug products are exempt, under certain conditions, from three key provisions of the Act: (1) the adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

On November 27, 2013, President Obama signed the Drug Quality and Security Act, legislation that contains important provisions relating to the oversight of compounding of human drugs. Title I of this law, the Compounding Quality Act, created a new section 503B of the FD&C Act under which a compounder can elect to register as an outsourcing facility. Registered outsourcing facilities can compound drugs without receiving patient-specific prescriptions or orders. If the conditions under section 503B of the FD&C Act are satisfied, drugs compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility qualify for exemptions from the new drug approval requirements (section 505 of the FD&C Act), the requirement to label products with adequate directions for use (section 502(f)(1) of the FD&C Act), and the Drug Supply Chain Security Act (section 582 of the FD&C Act). Outsourcing facilities remain subject to current good manufacturing practice (CGMP) requirements.

Both sections 503A and 503B require compounded drug products to satisfy several requirements to qualify for the statutory exemptions from the FD&C Act. One of those requirements is that the compounded drug product is not one that the Agency has identified as being demonstrably difficult to compound. *See* sections 503A(b)(3)(A); 503B(a)(6).

Specifically, section 503A states that the compounded drug product may not be one that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3)(A).

Similarly, section 503B states that the compounded drug, or category of drugs, either is not one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in

accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

FDA solicited nominations for drug products or categories of drug products that are considered difficult to compound in the Federal Register of December 4, 2013 (FDA-2013-N-1523-0001). Approximately 71 unique drug products or categories of drug products were nominated. (*See* attached list.) In addition, based on its experience reviewing new and abbreviated new drug applications, FDA is also identifying drug products or categories of drug products that are known to be difficult to manufacture, and, therefore, would also be considered difficult to compound. If an FDA-approved drug product is particularly difficult to manufacture, for example, because of the need for highly specialized equipment or processes, a comparable drug product would also be difficult to compound.

This document presents the criteria FDA proposes to consider in evaluating whether drug products or categories of drug products are demonstrably difficult to compound under sections 503A and 503B.

## **II. Proposed Criteria for Evaluating Candidates**

FDA has identified six criteria it proposes to use to evaluate whether drug products or categories of drug products are difficult to compound under sections 503A and 503B of the FD&C Act. The categories are not mutually exclusive. A drug product or category of drug products may meet one or more of these criteria that indicate it is a difficult to compound drug product or category of drug products. We propose to consider these criteria individually and collectively in deciding whether a drug product or category of drug products is difficult to compound under sections 503A and 503B of the FD&C Act.

FDA is proposing the following criteria for evaluating whether drug products or categories of drug products are difficult to compound under sections 503A and 503B of the FD&C Act:

### **1. Complex Formulation**

Complex formulation refers to a formulation in which the ingredients (active pharmaceutical ingredients (APIs) or excipients) are required to have certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product. For example, crystalline (including polymorphs) or amorphous forms, or chirality or particle size of an API might be critical in some formulations to the safety and efficacy of the drug product. The compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may also be evaluated to determine if the compounded drug product has a complex formulation. A complex formulation may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## 2. Complex Drug Delivery Mechanism

Complex drug delivery mechanism refers to the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect, such as passing through the stomach without dissolution and absorption or achieving permeation through the skin at a specific rate. Complex drug delivery mechanisms may include, for example, coated beads, polymeric matrices, or liposomes. A complex drug delivery mechanism may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## 3. Complex Dosage Form

Complex dosage form refers to physical dosage units with characteristics that are difficult to consistently achieve or maintain. Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system. Drug products may have very simple formulations, such as a single API, and a simple delivery mechanism, such as an injection, but the compounded drug product may be complex because the physical properties of the dosage form are difficult to achieve or maintain. Complex dosage forms may include, for example, propellant based aerosolized products or dry powder inhalers. A complex dosage form may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## 4. Bioavailability

Bioavailability refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Drug products may be considered difficult to compound if bioavailability is challenging to achieve because of the characteristics of the API or compounded formulation such as low permeability and/or low solubility. Bioavailability may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## 5. Compounding Process Complexity

Compounding process complexity refers to whether compounding the drug requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product. An example of a complex compounding process would include the multi-step and highly inter-related process of creating multi-particulate dosage forms of solid oral beads that require wet granulation, extrusion, spheronization, fluid bed drying, coating or curing before they are processed into the final dosage form. Compounding process complexity may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## 6. Physicochemical or Analytical Testing Complexity

Physicochemical or analytical testing complexity refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics. Drug products may demonstrate testing complexity when specialized analytical instruments and/or special training is necessary to show that the drug product will perform as expected. Performing cell-based assays for performance characterization (potency or permeability), and/or identifying constituents of complex mixtures by nuclear magnetic resonance, mass spectrometry, and/or X-ray powder diffraction (XRPD) could be considered examples of complex physicochemical or analytical testing. Physicochemical or analytical testing complexity may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

## Tab 7

# Drug Products That Employ Transdermal or Topical Delivery Systems

# Tab 7a

## Drug Products That Employ Transdermal or Topical Delivery Systems Nomination



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March 4, 2014

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**Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations; Docket Number FDA-2013-N-1523**

Dear Commissioner Hamburg and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, submits these comments in response to the Food and Drug Administration (FDA) request for nominations for Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA; Docket Number FDA-2013-N-1523).

We wish to express our concern that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding. Sections 503A and 503B of the FDCA, which create exemptions from new drug approval and other requirements for compounding pharmacies and outsourcing facilities, respectively, each separately authorize the FDA to publish a distinct list identifying drug products that present demonstrable difficulties for compounding and therefore

cannot be produced under the exemptions. We believe two separate lists are necessary, because drugs compounded at compounding pharmacies under a Section 503A exemption will be subject to reduced regulatory standards and fewer enforcement mechanisms relative to drugs compounded at outsourcing facilities under a Section 503B exemption. (Although it is important to note that drugs qualifying for either type of exemption will be subject to reduced requirements relative to drugs that undergo new drug approval, and therefore in general pose greater risk to patients than FDA-approved drugs).

We urge the FDA to classify products involving nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under 503A, but not under 503B. Production of drugs using this inherently high-risk process should be carried out only by a facility that is regularly inspected to verify compliance with current federal Good Manufacturing Practices (cGMP) requirements. Compounding pharmacies regulated under 503A are not required to follow cGMP, will rarely—if ever—be inspected by the FDA, and may or may not be regularly inspected by state officials, depending on the pharmacy regulations in each state, and any such state inspections are likely to be far less rigorous than those conducted by the FDA. By contrast, 503B outsourcing facilities, while not required to obtain new drug approval for their drug products, are nevertheless required to comply with cGMP and will be inspected by FDA officials on a risk-based schedule.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding, and to require such conditions for high-risk nonsterile-to-sterile compounding. Outsourcing facilities that register under Section 503B and comply fully with the FDCA will be permitted to compound such products, whereas compounding pharmacies regulated under 503A would not be allowed to compound such products.

We also recommend designation of several additional product categories as presenting demonstrable difficulties for compounding, and which therefore cannot be produced under 503B and/or 503A exemptions. A full list of product categories we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

## I. Regulatory Background and Relevant Statutory Authority

Section 503A of the FDCA, created under the Food and Drug Administration Modernization Act of 1997 (FDAMA),<sup>1</sup> describes the conditions under which a human drug product, compounded for an identified individual based on a prescription, is entitled to an exemption from the federal requirements for new drug approval, compliance with cGMP, and specific federal labeling requirements.<sup>2</sup> Rather than follow cGMP requirements, pharmacies qualifying for a 503A exemption must produce drug products under conditions that comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding, including USP Chapter 797, addressing sterile compounding.<sup>3,4</sup>

Pharmacies may qualify for a Section 503A exemption only when producing a drug product “not . . . identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.”<sup>5</sup> Section 503A requires that the FDA consult an advisory committee on pharmacy compounding prior to identifying such products, absent urgent public health need.<sup>6</sup>

Following passage of FDAMA, the FDA initiated an administrative process aimed at creating a list of drugs presenting demonstrable difficulties for compounding. In 2000, the FDA requested comments on a concept paper describing the agency’s preliminary thoughts on the matter (FDA Concept Paper).<sup>7</sup> However, these preliminary efforts were suspended following a 2002 Supreme Court decision holding portions of Section 503A unconstitutional.<sup>8</sup>

Regulation under Section 503A has been revived by the Drug Quality and Security Act of 2013, which verified the constitutionality of the portions Section 503A that had not been addressed in the Supreme Court’s 2002 decision, including the relevant sections addressing the difficult-to-compound list, by removing the provisions deemed unconstitutional by the Court.<sup>9</sup> The 2013 Act also added Section 503B to the FDCA, creating a new category of drug producers, known as

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<sup>1</sup> Pub. Law No. 105-115.

<sup>2</sup> FDCA Section 503A, *codified as* 21 U.S.C. § 353a.

<sup>3</sup> 21 U.S.C. § 353a (b)(1)(A)(i).

<sup>4</sup> Food and Drug Administration Draft Guidance: Pharmacy compounding of human drug products under Section 503A of the Federal Food, Drug and Cosmetics Act. December 2013.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf>. Accessed February 18, 2014.

<sup>5</sup> 21 U.S.C. § 353a (b)(3)(A).

<sup>6</sup> 21 U.S.C. § 353a (c)(1).

<sup>7</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>8</sup> 78 Fed. Reg. 72,840, 72,840 (Dec 4, 2013).

<sup>9</sup> *Ibid.*

“outsourcing facilities.”<sup>10</sup> Like compounding pharmacies regulated under 503A, outsourcing facilities that qualify for Section 503B are exempt from new drug approval and specific federal labeling requirements, and are therefore subject to lighter federal regulation than manufacturers of FDA-approved drugs. However, unlike Section 503A compounding pharmacies, Section 503B outsourcing facilities will be required to comply with cGMP. Outsourcing facilities must also comply with additional requirements, including federal registration and periodic reporting requirements, as well as federal inspections of facilities and records, conducted on a risk-based schedule.

Like Section 503A, Section 503B excludes drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs.<sup>11</sup> However, rather than cross-reference the same list of products identified under Section 503A, Section 503B outlines distinct procedural steps for the FDA to follow in identifying drugs that are difficult to compound, including a specific timeline and process for creating a list of such products.<sup>12</sup> Section 503B also requires the FDA to “tak[e] into account the risks and benefits to patients” when identifying products for the list and authorizes the agency to identify “conditions that are necessary to prevent the drug or category of drugs from presenting demonstrable difficulties [for compounding].”<sup>13</sup>

Neither Section 503A nor Section 503B require that the FDA develop and publish a single list of drug products that present demonstrable difficulties for compounding. If anything, Congress, having identified two distinct processes and two slightly different sets of requirements and authorities for each section, appears to have contemplated that the FDA would create two separate lists. Moreover, even if two separate lists are not statutorily required, the FDA can certainly exercise its discretion to promulgate two separate lists. Separate lists would represent sound public health policy because the conditions for compounding in each type of facility are markedly different, with 503A compounding pharmacies subject to significantly lower regulatory standards than 503B outsourcing facilities.

Alternatively, if the FDA proceeds with its proposed plan to promulgate only one list, the agency has the authority to identify compliance with 503B and cGMP requirements as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding. Outsourcing facilities that register under Section 503B and comply fully with cGMP would then be permitted to compound such products, whereas compounding pharmacies that qualify for exemption under 503A that have not verified compliance with cGMP would not be allowed to compound such products.

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<sup>10</sup> Section 503B, *not yet codified*. Pub. Law 113-54. -

<sup>11</sup> Pub. Law 113-54. Sec. 503B (a)(6). -

<sup>12</sup> Pub. Law 113-54. Sec. 503B (c)(2). -

<sup>13</sup> Pub. Law 113-54. Sec. 503B (a)(6). -

## II. Specific Drug Product Categories

We propose six categories of drug products for placement on the list or lists of products presenting demonstrable difficulties for compounding under Sections 503B and/or 503A.

### 1. Nonsterile-to-sterile compounding

Certain drugs must be sterile (in other words, free from all living microorganisms) in order to be administered safely. These include dosage forms administered parenterally (injections, infusions, or implants), aqueous-based inhalation solutions, and ophthalmic products.<sup>14</sup> As stated in the 2000 FDA Concept Paper, “[s]terility is absolute and should never be considered in a relative manner -- a product cannot be partially or almost sterile.”<sup>15</sup>

Problems that develop in compounding sterile products can have serious and far-reaching consequences for patient safety. In September 2012, the Centers for Disease Control and Prevention (CDC) and the FDA announced the beginning of what would become the largest outbreak of infection linked to a medical product in more than four decades: healthcare facilities in 23 states received three lots of contaminated preservative-free injectable methylprednisolone acetate produced by the New England Compounding Center (NECC), a compounding pharmacy in Framingham, Massachusetts.<sup>16</sup> Over the next year, the CDC tracked 751 cases of infection, including meningitis, paraspinal/spinal infection, stroke, and joint infection. Sixty-four of those cases resulted in death.<sup>17</sup>

While the NECC-linked outbreak was by far the largest ever associated with a compounding pharmacy, it was by no means an isolated event. Table 1 contains a list of infection outbreaks linked to compounding pharmacies since 2004. Many more small-scale outbreaks or isolated infections caused by compounded products likely went undetected because the source of such infections is often not suspected or challenging to identify.

**Table 1: Infection Outbreaks Associated with Compounded Products, 2004-2013**

Date of Outbreak	Type of Injury	Pharmacy	Source
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<sup>14</sup> Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>15</sup> *Ibid.*

<sup>16</sup> Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – healthcare facilities. October 23, 2013. <http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html>. Accessed February 21, 2014.

<sup>17</sup> Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – case count. October 23, 2013. [http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount\\_table](http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table). Accessed February 21, 2014.

Dec 2004 – Feb 2005	Bloodstream infections; 36 cases, including at least 13 children	Anonymous	CDC2005 <sup>18</sup>
Jun – Jul 2004	Bloodstream infections; 2 children	Anonymous	Held2006 <sup>19</sup>
Jan – Mar 2005	11 cases of bacteremia, including 5 cases of sepsis	PharMEDium	CDC2005 <sup>20</sup>
Mar 2005	6 cases of sepsis; 1 resulting in death	PharMEDium	FDA2007(1) <sup>21</sup>
Dec 2004 – Aug 2005	Eye infection resulting in permanent loss of vision; 6 cases	Anonymous	Sunenshine2009 <sup>22</sup>
Dec 2006	70 complaints indicating signs of infection	Med-South Pharmacy	FDA2007(2) <sup>23</sup>
Oct – Nov 2007	7 bloodstream infections	Anonymous	Maragakis2009 <sup>24</sup>
Mar 2011	19 bloodstream infections	Meds IV	FDA2011 <sup>25</sup>
Jul 2011	12 eye infections; 11 resulting in vision loss	Infupharma	Goldberg2013 <sup>26</sup>
Aug 2011 – Mar 2012	47 eye infections; 39 resulting in vision loss	Franck's Compounding Lab	Mikosz2014 <sup>27</sup>

<sup>18</sup> Centers for Disease Control. Pseudomonas bloodstream infections associated with a heparin/saline flush --- missouri, new york, texas, and michigan, 2004—2005. *MMWR* 2005;54(11):269-272. - <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm>. Accessed February 26, 2014. -

<sup>19</sup> Held MR, BegierEM, Beardsley DS, et al. Life-threatening sepsis caused by *Burkholderia cepacia* from - contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. *Pediatrics* - 2006;118(1):e212-5. -

<sup>20</sup> Centers for Disease Control. Health Advisory: *Serratia marcescens* blood stream infections associated with - contaminated magnesium sulfate solutions. March 18, 2005. - [http://www.randolphcountyhealth.org/docs/educ/pr/031805\\_CDC.html](http://www.randolphcountyhealth.org/docs/educ/pr/031805_CDC.html). Accessed February 21, 2014. -

<sup>21</sup> Food and Drug Administration. Warning Letter to PharMEDium. April 13, 2007. - <http://www.fda.gov/oc/ice/enforcementactions/warningletters/2007/ucm076357.htm>. Accessed February 21, - 2014. -

<sup>22</sup> Sunenshine R, Schultz M, Lawrence MG, et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. *Clin Infect Dis* 2009;48:1580-3. -

<sup>23</sup> Food and Drug Administration. Warning Letter to Med-South Pharmacy. September 28, 2007. - <http://www.fda.gov/oc/ice/enforcementactions/warningletters/2007/ucm076516.htm>. Accessed February 21, - 2014. -

<sup>24</sup> Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated - with contaminated intravenous fentanyl. *Emerg Infect Dis* 2009;15(1):12-18. -

<sup>25</sup> Food and Drug Administration. CDC and ADPH investigate outbreak at Alabama hospitals; products recalled. - March 29, 2011 (republished from Alabama Department of Public Health). - <http://www.fda.gov/safety/recalls/archiverecalls/2011/ucm249068.htm>. Accessed February 21, 2014. -

<sup>26</sup> Goldberg RA, Flynn HW, Miller D, et al. *Streptococcus* endophthalmitis outbreak after intravitreal injection of - Bevacizumab: One-year outcomes and investigative results. *Ophthalmology* 2013; 120(7):1448-53. -

<sup>27</sup> Mikosz CA, Smith RM, Kim M, et al. Fungal endophthalmitis associated with compounded products. *Emerg Infect Dis* 2014;20(2):248-256. -

Mar 2013	5 eye infections	Clinical Specialties	FDA2013(1) <sup>28</sup>
May 2013	7 skin abscesses	Main Street Family Pharmacy	FDA2013(2) <sup>29</sup>

In addition to being free of microorganisms, injectable compounded pharmaceuticals must also be free from pyrogens (the byproducts of microorganisms that can cause reactions when introduced into humans) and particulate matter, which can cause harmful blood clots, particularly when a product is administered in large quantities.<sup>30</sup>

Sterile-to-sterile compounding, described as “low” or “medium” risk compounding by the U.S. Pharmacopeial Convention, involves manipulating sterile ingredients entirely within an ISO Class 5 or better environment (a “clean room” carefully controlled to exclude microbial growth) using only sterile ingredients, products, components, and devices.<sup>31</sup> Depending on the number of sterile products and aseptic manipulations involved, sterile-to-sterile compounding may involve low or medium risk of microbial contamination.<sup>32</sup>

Nonsterile-to-sterile compounding, described as “high” risk compounding by the U.S. Pharmacopeial Convention, involves compounding using nonsterile ingredients or materials, including nonsterile active pharmaceutical ingredients (API), finished FDA-approved products not intended for sterile routes of administration (e.g., oral), or nonsterile devices or packaging.<sup>33</sup> It also includes sterile contents of commercially manufactured products that have been exposed to conditions that would render them nonsterile (e.g., exposure to air quality worse than ISO Class 5 for more than one hour). To engage in this process safely, an appropriate sterilization method must be used to ensure that such products are sterile and free of pyrogens and particulate matter prior to distribution.<sup>34</sup>

The high-risk process of nonsterile-to-sterile compounding is not appropriate for compounding pharmacies exempt under Section 503A, as these entities are not held to cGMP standards and

<sup>28</sup> Food and Drug Administration. Clinical Specialties Compounding Pharmacy announces voluntary nationwide - recall of all lots of sterile products repackaged and distributed by Clinical Specialties Compounding due to lack of - sterility assurance. March 20, 2013. <http://www.fda.gov/safety/recalls/ucm344786.htm>. Accessed February 21, - 2014. -

<sup>29</sup> Food and Drug Administration. Main Street Pharmacy, LLC issues voluntary nationwide recall of all sterile - compounded products. May 28, 2013. <http://www.fda.gov/safety/recalls/ucm354182.htm>. Accessed February 21, - 2014. -

<sup>30</sup> Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for - Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments-to-the-FDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

<sup>31</sup> <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

<sup>32</sup> *Ibid.*

<sup>33</sup> *Ibid.*

<sup>34</sup> *Ibid.*

instead must comply with USP standards only. USP standards for sterile compounding, laid out in Chapter 797 of the USP, are set by the U.S. Pharmacopeial Convention, a private organization that sets standards for drugs, food ingredients, and dietary supplements.<sup>35</sup> While USP standards have advanced over time, they remain relatively lax compared to the cGMP standards developed and enforced by the FDA. One key difference is that cGMP requires a drug manufacturer to validate and periodically re-validate each step in the production process through direct testing, whereas USP Chapter 797 routinely allows pharmacists to base production design on review of available literature and the pharmacist's prior experience.

For example, in determining sterilization methods, cGMP requires that any sterilization process used to prevent microbial contamination be validated through appropriate direct studies,<sup>36</sup> and offers detailed guidance on the design and conduct of such validation studies.<sup>37</sup> Once production begins, a single contaminated product in any batch smaller than 5,000 should trigger an investigation and revalidation of the entire manufacturing process.<sup>38</sup> USP, by contrast, does not generally require product-specific validation, instead allowing the pharmacist to select a method based on "experience and appropriate information sources," stating that the sterilization method should "preferably" be verified "whenever possible."<sup>39</sup>

Similarly, federal cGMP regulations require a detailed written stability testing program to determine appropriate storage conditions and expiration dates.<sup>40</sup> By contrast, USP describes the practice of establishing "beyond use dating (BUD)," and the especially high-risk practice of "theoretical beyond use dating," both of which can be based on a review of general literature and do not require direct product testing.<sup>41</sup> The USP acknowledges that "[t]heoretically predicted beyond-use dating introduces varying degrees of assumptions and, hence, a likelihood of error or at least inaccuracy," yet USP Chapter 797 does not require direct stability testing to avoid such problems. Indeed, actual testing is only "strongly urged" to support dating periods exceeding 30 days.<sup>42</sup>

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<sup>35</sup> U.S. Pharmacopeial Convention. <http://www.usp.org/about-usp>. Accessed February 28, 2014. -

<sup>36</sup> 21 CFR 211.113(b). -

<sup>37</sup> Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

<sup>38</sup> Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

<sup>39</sup> <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

<sup>40</sup> 21 CFR § 211.166. ("There shall be a written testing program designed to assess the stability characteristics of - drug products. The results of such stability testing shall be used in determining appropriate storage conditions and - expiration dates. The written program shall be followed and shall include: (1) Sample size and test intervals based - on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for - samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in - the same container-closure system as that in which the drug product is marketed; (5) Testing of drug products for - reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.") -

<sup>41</sup> <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

<sup>42</sup> *Ibid.*

We are aware that the FDA previously issued a preliminary conclusion in its Concept Paper published in 2000, which indicated that sterile compounding could be carried out by compounding pharmacies compliant with USP requirements for sterile compounding.<sup>43</sup> We urge the FDA to reconsider this preliminary conclusion, which addressed all sterile compounding, rather than focusing separately on, and requiring more stringent standards for, especially high-risk nonsterile-to-sterile compounding.

The FDA's earlier preliminary conclusion was also based in part on a perceived "substantial need for compounded sterile products, especially in the area of extemporaneous compounding."<sup>44</sup> While a general need for extemporaneously compounded sterile products may have existed under the conditions that the FDA considered in 2000, no substantial need exists for high-risk nonsterile-to-sterile compounding to be performed in compounding pharmacies exempt under Section 503A. First, most needs for sterile compounded products can be met through modifying federally regulated commercially available sterile products, a low- to medium-risk form of sterile compounding, rather than through high-risk compounding from nonsterile-to-sterile ingredients. Second, following the passage of the Drug Quality and Security Act, any residual needs requiring nonsterile-to-sterile compounding (in other words, making products from bulk API rather than modifying FDA-approved sterile products) are more appropriately met by carrying out such high-risk compounding in outsourcing facilities compliant with Section 503B and federal cGMP requirements (as opposed to relying on 503A compounding pharmacies exempt from cGMP requirements).

Furthermore, more information is now available on the actual conditions of practice in compounding pharmacies, historically subject to minimal federal oversight. Recent FDA inspections of compounding pharmacies have revealed widespread sterility concerns, some of which may violate USP standards in addition to cGMP standards, suggesting that the safety of high-risk nonsterile-to-sterile compounding cannot be assured without increased federal oversight.<sup>45</sup> Some of these violations are discussed in greater detail below.

Companies that have registered as outsourcing facilities under Section 503B will now be held to higher federal standards, and we hope that conditions in these facilities will improve. However, the FDA cannot reasonably expect these conditions to improve substantially in compounding pharmacies exempt from federal oversight under Section 503A, as the current regulatory environment does not provide for appropriate oversight of compounding pharmacies that qualify for this exemption. While the FDA does have authority to inspect and take enforcement action against compounding pharmacies for violations of federal law, the agency has no plans to carry

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<sup>43</sup> Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>44</sup> *Ibid.*

<sup>45</sup> Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

out regular inspections, leaving day-to-day oversight up to state boards of pharmacy.<sup>46</sup> Many compounding pharmacies are not routinely monitored by state boards to verify compliance with USP Chapter 797 requirements for sterile compounding. A 2012-2013 survey of state boards of pharmacy published by the office of U.S. Rep. Edward J. Markey (now Senator Markey), indicated that 37 state boards of pharmacy do not routinely track which pharmacies are providing sterile compounding services, and only 19 state boards of pharmacy provide inspectors with special training to identify problems with sterile compounding.<sup>47</sup>

For these reasons, as well as our comments on more specific factors below, we urge the FDA to identify nonsterile-to-sterile compounding as a category presenting demonstrable difficulties for compounding under Section 503A, but not necessarily Section 503B.

The FDA has requested comment on specific relevant factors, including the complexity of compounding, facilities and equipment, personnel training, and testing and quality assurance. We now address each of these factors in turn with regard to nonsterile-to-sterile compounding:

### *Complexity of Compounding*

Nonsterile-to-sterile compounding involves extremely complex production processes. As stated in the FDA's Concept Paper:

The preparation of sterile products is often unavoidably complex, involving many steps and manipulations. Each step poses an opportunity for microbial contamination. The manipulation of a sterile drug product may contaminate it, especially when nonsterile components are used (e.g., if the product is packaged into a nonsterile syringe or vial purported to be sterile), nonsterile equipment is used, or novel, complex, or prolonged aseptic processes are employed.<sup>48</sup>

Even a relatively small change in the production process, such as a switch to new packaging material, may result in unanticipated and far-reaching consequences. The largest infection outbreak associated with a pharmaceutical product in United States history occurred as the result of one such seemingly minor change: Between April and September 1970, Abbott Laboratories began phasing in a new type of cap liner that relied on synthetic plastic, rather than natural

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<sup>46</sup> Food and Drug Administration. Compounding and the FDA: Questions and Answers. December 2, 2013. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm#regulates>. Accessed February 24, 2014. -

<sup>47</sup> Report of the US House of Representatives. State of Disarray. How states' inability to oversee compounding pharmacies puts public health at risk. April 15, 2013. -

<sup>48</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentsToTheFDCAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

rubber.<sup>49</sup> The rubber previously used in the caps had antibacterial properties that synthetic liners lacked. Inadequate environmental control and sampling protocols contributed to microbial contamination of the liners, which thrived on the new synthetic medium. The result was catastrophic: Abbott Laboratories distributed approximately 45 percent of all intravenous fluids sold in the United States at the time, and the outbreak is estimated to have led to between 2,000 and 8,000 cases of infection, and between 200 and 800 deaths.<sup>50</sup>

Both USP and cGMP standards have been updated dramatically over the ensuing decades, yet complex production processes remain challenging to monitor.<sup>51</sup> Any change in the production process should be validated through direct testing to ensure that it does not result in unforeseen consequences. This type of direct validation can only be ensured in facilities verified as fully compliant with cGMP. Nonsterile-to-sterile compounding, therefore, presents demonstrable difficulties for compounding under any other conditions.

### *Facilities and Equipment*

Nonsterile-to-sterile compounding requires sophisticated facilities and equipment that must be maintained to rigorous standards. As stated in the FDA's concept paper:

To maintain the essential characteristics of sterile products (i.e., sterility and freedom from particulate matter and pyrogens), the products and their components must be manipulated in a suitable environment using aseptic techniques. ... It is important to minimize bioburden during the production process even when terminal sterilization is used. Therefore, the production facilities and associated procedures must meet exacting standards.<sup>52</sup>

While USP and cGMP have developed harmonized standards regarding appropriate levels of bioburden (the accumulation of potential biological contaminants during the production process) in the environment, recent FDA inspections of compounding pharmacies have revealed repeated failures in maintaining the environmental monitoring necessary to meet these standards. In 2013, FDA inspectors cited dozens of compounding pharmacies for failing to assess airflow patterns with adequate smoke studies performed under dynamic conditions and/or failing to conduct appropriate environmental monitoring.<sup>53</sup> While FDA inspectors focused on violations of cGMP

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<sup>49</sup> Centers for Disease Control. Epidemiologic notes and reports nosocomial bacteremias associated with intravenous fluid therapy – USA. MMWR Weekly. December 26, 1997/46(51);1227-1233.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00050554.htm>. Accessed February 18, 2014.

<sup>50</sup> *Ibid.*

<sup>51</sup> *Ibid.*

<sup>52</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>53</sup> Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

standards, many of the conditions identified would be unacceptable under either cGMP or USP standards. For example, FDA inspectors also noted visible dust, stains, splatters, residue, rust, live or dead insects, and other sources of potential contamination in a disturbing number of facilities.<sup>54,55,56,57,58,59,60,61,62</sup>

Some of the pharmacies cited by FDA inspectors in 2013 have subsequently registered as outsourcing facilities.<sup>63</sup> While we remained concerned that outsourcing facilities will not be required to undergo new drug approval or verify compliance with cGMP prior to producing sterile products, we assume that the FDA will make every effort to ensure that these facilities comply with cGMP standards moving forward. (If this assumption proves to be incorrect, then nonsterile-to-sterile compounding by outsourcing facilities will also pose unacceptable risks to patients.)

By contrast, many pharmacies that have not registered as outsourcing facilities continue to claim that their compounding facilities adequately comply with applicable state and USP standards

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<sup>54</sup> Food and Drug Administration. Axiom Healthcare Pharmacy dba Balanced Solutions Compounding. March 15, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

<sup>55</sup> Food and Drug Administration. 483 Inspection Report. Custom Compounding Centers, LLC. December 13, 2012. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM348232.pdf>. Accessed February 24, 2014. -

<sup>56</sup> Food and Drug Administration. 483 Inspection Report: Anazahealth Corporation. February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM341368.pdf>. Accessed February 24, 2014. -

<sup>57</sup> Food and Drug Administration. 483 Inspection Report: University Pharmacy, Inc. February 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM342275.pdf>. Accessed February 24, 2014. -

<sup>58</sup> Food and Drug Administration. 483 Inspection Report: College Pharmacy Incorporated. March 15, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM345701.pdf>. Accessed February 24, 2014. -

<sup>59</sup> Food and Drug Administration. 483 Inspection Report: The Compounding Shop, Inc. March 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM345933.pdf>. Accessed February 24, 2014. -

<sup>60</sup> Food and Drug Administration. 483 Inspection Report: Pentec Health, Inc. April 1, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM346817.pdf>. Accessed February 24, 2014. -

<sup>61</sup> Food and Drug Administration. 483 Inspection Report: Pallimed Solutions, Inc. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM348236.pdf>. Accessed February 24, 2014. -

<sup>62</sup> Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services, Inc. February 19, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM348237.pdf>. Accessed February 24, 2014. -

<sup>63</sup> Food and Drug Administration. Registered Outsourcing Facilities. Updated as of February 21, 2014. - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>. - Accessed February 28, 2014. -

even when they have been informed by the FDA of sterility concerns, making them unlikely to adjust their practices or upgrade their current facilities. In fact, one pharmacy, NuVision, recently refused a request by the FDA to recall all sterile products after the agency identified safety concerns related to sterility during a facility inspection.<sup>64,65</sup> The pharmacy still claims on its website to adhere to USP standards for sterile compounding.<sup>66</sup> In addition, three other compounding pharmacies have responded following FDA inspections with their opinion (without citing verification by independent inspectors) that the current facilities satisfy USP requirements, in spite of the fact that federal inspectors had identified serious sterility concerns.<sup>67,68,69</sup> Regardless of whether these pharmacies do, in fact, comply with USP requirements (a claim that has not been confirmed through independent inspections), it is clear that they are unlikely to dramatically upgrade their facilities in the near future. Appropriately, at least one of these compounding pharmacies has reported that it does not engage in nonsterile-to-sterile compounding.<sup>70</sup> We urge the FDA to ensure that all compounding pharmacies exempt under 503A avoid this type of high-risk compounding, which cannot be performed safely except in a facility that has been regularly inspected for compliance with cGMP standards.

### *Personnel Training*

Specialized, highly technical training is essential to ensure proper compounding of nonsterile-to-sterile drug products. As stated in the FDA's Concept Paper:

The processes used in pharmacies to prepare sterile products are highly personnel-intensive. The contamination of pharmacy-prepared products (e.g., intravenous admixtures and prefilled syringes) by aseptic processing most likely will be caused by personnel-associated factors. These factors may include the shedding of contaminants from people into the controlled environment, improper procedures under laminar air flow, and the use of poor aseptic technique. Therefore, pharmacy personnel involved in compounding

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<sup>64</sup> FDA reminds health care providers not to use sterile products from NuVision Pharmacy. August 16, 2013. - <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm365402.htm>. Accessed February 26, 2014. -

<sup>65</sup> Food and Drug Administration. Warning Letter. NuVision Pharmacy. Jul 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM363761.pdf>. Accessed February 28, 2014. -

<sup>66</sup> Nuvision. Sterility Testing. <http://nuvisionpharmacy.com/sterility-testing/>. Accessed February 26, 2014. -

<sup>67</sup> Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014. -

<sup>68</sup> IV Solutions of Lubbock. Response Letter to the Food and Drug Administration. April 25, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349813.pdf>. Accessed February 24, 2014. -

<sup>69</sup> Pharmacy Creations. Response Letter to the Food and Drug Administration. September 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM371359.pdf>. Accessed February 24, 2014. -

<sup>70</sup> Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014.

sterile products must have sufficient knowledge, training, and experience to perform the task correctly and safely. Furthermore, a pharmacy's quality assurance program for sterile products must include requirements that personnel consistently adhere to performance standards; that performance problems be monitored, detected, and corrected; and that personnel undergo initial and periodic certification.<sup>71</sup>

Appropriate training is essential to ensure that sterile solutions do not become contaminated during preparation. A study of pharmacy students by Isanhart et al, published in 2008, assessed procedures performed at the beginning and end of a 16-week parenterals laboratory course offering instruction in aseptic technique.<sup>72</sup> Prior to undergoing training, 21 of 504 syringes (4 percent) prepared by the students were contaminated during media fill tests, a number that was reduced to 0 of 498 by the end of the course.

While zero contamination is clearly possible with appropriate technique, reports from the FDA and published literature suggest that use of inadequate technique is widespread. Rates of contamination during medium and low risk compounding operations remain highly variable and unacceptably high in practice, ranging from 0 percent to over 6 percent among experienced, practicing pharmacists and technicians.<sup>73,74,75,76,77</sup> FDA inspection reports from 2013 also document numerous examples of inappropriate aseptic technique and inadequate monitoring of pharmacy personnel. Observations included inadequate gowning that leaves skin exposed, failure to adequately monitor employees for microbial contamination during aseptic operations, uncontrolled movement of employees in and out of the ISO Class 5 clean room where sterile drugs are prepared, inappropriate use of nonsterile objects in aseptic operations, and failure to adequately clean and sanitize equipment and surfaces in the clean room.<sup>78,79,80,81</sup> Such high-risk

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<sup>71</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons - of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendments-to-the-FDCAAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

<sup>72</sup> Isanhart CM, McCall KL, Kretschmer D, Grimes BA, Parenterals laboratory course to reduce microbial contamination rates in media fill tests performed by pharmacy students. *Am J Pharm Educ.* 2008;72(2):27. -

<sup>73</sup> Reiter PD. Sterility of intravenous fat emulsion in plastic syringes. *Am J Health Syst Pharm* 2002;59:1857-9. -

<sup>74</sup> van Grafhorst JP, Foudraine NA, Nooteboom F, Crombach WH, Oldenhof NJ, van Doorne H. Unexpected high risk - of contamination with staphylococci species attributable to standard preparation of syringes for continuous - intravenous drug administration in a simulation model in intensive care units. *Crit Care Med.* 2002;30:833-6. -

<sup>75</sup> Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-5. -

<sup>76</sup> Thomas M, Sanborn M, Couldry R. IV admixture contamination rates: traditional practice site versus a class 100 cleanroom. *Am J Health-Syst Pharm.* 2005;62:2386-92.

<sup>77</sup> Trissel LA, Gentempo JA, Anderson RW, Lajeunesse JD. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005;62:285-8. -

<sup>78</sup> Food and Drug Administration. 483 Inspection Report: Avella of Deer Valley, Inc. February 25, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM342276.pdf>. Accessed February 26, 2014. -

<sup>79</sup> Food and Drug Administration. 483 Inspection Report: FVS Holdings, Inc. dba Green Valley Drugs. March 15, - 2013. -

nonsterile-to-sterile compounding by improperly trained personnel poses unacceptable risk to patients. To avoid this risk, nonsterile-to-sterile compounding must be carried out only in facilities that are regularly inspected for compliance with cGMP.

### *Testing and Quality Assurance*

Testing and quality assurance are especially important in nonsterile-to-sterile compounding as a means of verifying that sterility has been successfully achieved. As the FDA stated in its Concept Paper:

All compounded sterile products should be inspected prior to use in patients. Low-risk compounded sterile products (e.g., sterile products prepared from sterile components using proper techniques and equipment) should, at a minimum, be inspected physically and visually for cloudiness and particulate matter. High-risk compounded sterile products (e.g., sterile products prepared from nonsterile components using proper techniques and equipment) should undergo end-product sterility and pyrogen testing before they are dispensed from the pharmacy.<sup>82</sup>

Sterility testing is required under cGMP, with samples taken at the beginning, middle, and end of the aseptic processing operation.<sup>83</sup> Any positive test result is considered a serious cGMP issue requiring thorough investigation.<sup>84</sup> Under USP standards, only high-risk sterile products prepared in groups of 25 or more or that are exposed to certain temperatures for varying lengths of time must be tested for sterility prior to release, and the pharmacy need not await test results before dispensing the products to patients.<sup>85</sup> Moreover, products intended for inhalation or ophthalmic administration need not be tested for bacterial endotoxins (pyrogens) prior to release.<sup>86</sup>

As might be expected, a disturbing number of compounding pharmacies forgo testing and quality assurance measures that would be required under cGMP. FDA inspection reports of

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<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM348241.pdf>. Accessed February 26, 2014. -

<sup>80</sup> Food and Drug Administration. University Pharmacy, Inc. February 26, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM342275.pdf>. Accessed February 26, 2014. -

<sup>81</sup> Food and Drug Administration. 483 Inspection Report: Lowlyn Pharmacies, Inc. March 8, 2013.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM345695.pdf>. Accessed February 26, 2014. -

<sup>82</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons - of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

<sup>83</sup> Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

<sup>84</sup> *Ibid.*

<sup>85</sup> <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.

<sup>86</sup> *Ibid.*

compounding pharmacies in 2013 identified widespread failure to conduct sterility, endotoxin, and potency testing on all end products. Many pharmacies also failed to document adequate investigation after identifying particulates, discoloration, microbial contamination, leaking product, or other issues with finished samples. In two cases, particulate matter was discovered in products from lots that had already been shipped to customers.<sup>87,88</sup> Half a dozen pharmacies were also cited for failing to adequately follow up on complaints, including reports indicating mislabeling, particulate matter, and other serious concerns with drug products, including fever, injection-site redness, abscess, and other disturbing adverse events in patients.<sup>89,90,91,92,93,94</sup>

Based on the factors identified above, high-risk nonsterile-to-sterile compounding cannot be conducted safely in compounding pharmacies that are not regularly inspected for full compliance with cGMP standards. We therefore urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Section 503A, but not necessarily Section 503B.

Alternatively, if the FDA creates a single unified list, we urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for

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<sup>87</sup> Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

<sup>88</sup> Food and Drug Administration. 483 Inspection Report: Axiom Healthcare Pharmacy dba Balanced Solutions - Compounding. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

<sup>89</sup> Food and Drug Administration. 483 Inspection Report: MedPREP Consulting, Inc. April 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348230.pdf>. Accessed February 24, 2014. -

<sup>90</sup> Food and Drug Administration. 483 Inspection Report: Wedgewood Village Pharmacy, Inc. February 11, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342543.pdf>. Accessed February 24, 2014. -

<sup>91</sup> Food and Drug Administration. 483 Inspection Report: PharMEDium Services LLC (Parsippany, NJ). February 28, - 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342271.pdf>. Accessed February 24, 2014. -

<sup>92</sup> Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

<sup>93</sup> Food and Drug Administration. 483 Inspection Report: NuVision Pharmacy, Inc. April 17, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348772.pdf>. Accessed February 24, 2014. -

<sup>94</sup> Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services (Chicago, IL). - February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM341365.pdf>. Accessed February 24, 2014.

compounding except under conditions present in outsourcing facilities compliant with Section 503B and cGMP requirements.

## 2. Metered dose inhaler (MDI) products

The FDA's Concept Paper published in 2000 recommended that MDI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

The MDI is one of the most complicated drug delivery systems currently marketed by the pharmaceutical industry ...MDI products are primarily used by patients suffering from chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Individuals suffering from asthma and COPD tend to have airways that are hyper-reactive to inhalants. It is therefore critical that the contents and the delivery characteristics of MDI products be carefully controlled to ensure that the product will be safe and effective. Even slight changes in the formulation, drug substance particle size, valve, or actuator can have a major effect on the aerosol delivery and potency characteristics. This effect can significantly alter the safety and effectiveness of the device. For example, a change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs.<sup>95</sup>

The FDA concluded that MDI products present demonstrable difficulties in compounding because:

- Metered dose inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of MDI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.<sup>96</sup>

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<sup>95</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>96</sup> *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to MDI products and urge the agency to identify MDI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

### 3. Dry powder inhaler (DPI) products

The FDA's Concept Paper published in 2000 also recommended that DPI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

DPIs are complex drug products that differ in many aspects from more conventional drug products. ... There is a wide array of potential DPI designs, all complex in their design and function and many with characteristics unique to the particular design.

Regardless of design, the most crucial attributes of DPIs are the reproducibility of the dose and particle size distribution. It is difficult to maintain these qualities through the expiration date and to ensure the functionality of the device during the period of patient use. The unique characteristics of DPIs must be considered in their preparation, particularly with respect to the product's formulation, container closure system, and testing.<sup>97</sup>

The FDA concluded that DPI products present demonstrable difficulties in compounding because:

- Dry powder inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and the product-to-product uniformity that is critical for dosing accuracy is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of DPI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.<sup>98</sup>

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<sup>97</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendmentsToTheFDCAAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>98</sup> *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to DPI products, and urge the agency to identify DPI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

#### 4. Transdermal Delivery Systems (TDSs)

Finally, the FDA's Concept Paper published in 2000 recommended that TDS products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

TDS products are complex to develop and may require the use of new technologies. Each system is formulated to meet specific biopharmaceutical and functional criteria. The materials of construction, configurations, and combination of the drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and matched to optimize adhesive properties and drug delivery requirements. The equipment and the technology required for the manufacture of TDS products limit their preparation to properly equipped manufacturers.<sup>99</sup>

The FDA concluded that TDS products present demonstrable difficulties in compounding because:

- TDSs are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of TDS products is complex.
- Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products.
- Specialized technical training is essential to ensure proper compounding of TDS products
- Sophisticated, difficult to perform testing of the compounded product is required to ensure potency, purity, and quality of the drug product prior to dispensing.<sup>100</sup>

We agree with the FDA's prior analysis and conclusions with respect to TDS products and urge the agency to identify TDS products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

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<sup>99</sup> FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

<sup>100</sup> *Ibid.*

## 5. Sustained or time-release dosage forms

Public Citizen previously submitted comments on the FDA's Concept Paper published in 2000.<sup>101</sup> In those comments, we recommended that the FDA evaluate sustained or time-release dosage forms for categorization as products presenting demonstrable difficulties for compounding. As we stated previously:

Because there is no requirement to test [compounded sustained or time-release] products, it is no known if 90 percent of the active ingredient is released within the first 30 minutes after the dose is taken, or if 90 percent of the active ingredient remains in the dosage form after the dose is taken.<sup>102</sup>

Variation in rates of release of the active ingredient could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to ensure appropriate bioavailability for sustained or time-release dosage forms. Such clinical testing is not required under either Section 503A or Section 503B and can only be required for drug products that undergo premarket approval by the FDA. We therefore urge the FDA to categorize sustained or time-released dosage forms as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

## 6. Enteric-coated preparations

Public Citizen also previously recommended that the FDA evaluate enteric-coated preparations for categorization as products presenting demonstrable difficulties for compounding.<sup>103</sup> Enteric-coated preparations are preparations intended for drugs that are either destroyed by gastric acidity or that cause gastric irritation. As we previously stated, "enteric-coated preparations may, if not properly formulated, resist dissolution in the intestine, and very little if any of the active drug may be absorbed into the blood stream."<sup>104</sup>

As with sustained-release dosage forms, improperly formulated enteric-coated preparations could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to prevent these problems. Because such testing is not required under either Section 503A or Section 503B, we urge the FDA to categorize enteric-coated preparations as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

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<sup>101</sup> Public Citizen. Comments on Drugs that Present Difficulties for Compounding. August 2, 2000.

<http://www.citizen.org/Page.aspx?pid=3626>. Accessed March 3, 2014.

<sup>102</sup> *Ibid.*

<sup>103</sup> *Ibid.*

<sup>104</sup> *Ibid.*

### III. Conclusion

We are concerned that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding, and urge the agency to withdraw its proposal and instead develop two separate lists. Drugs compounded at compounding pharmacies under a Section 503A exemption should be treated differently than those subject to Section 503B, as the regulations governing each category of facility are different.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding.

Regardless of whether one or two lists is used, we urge the FDA to classify high-risk nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under compounding pharmacies exempt under Section 503A, but not necessarily outsourcing facilities exempt under 503B. This high-risk process may be safely carried out only by a facility that is regularly inspected to verify compliance with federal cGMP requirements.

We have also recommended designation of several additional product categories as presenting demonstrable difficulties for compounding.

A full list of product categories that we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

Thank you for your consideration of these comments.

Sincerely,



Sarah Sorscher, J.D., M.P.H.  
Attorney  
Public Citizen's Health Research Group

A handwritten signature in black ink, appearing to read "Michael Carome". The signature is fluid and cursive, with a long horizontal stroke at the end.

Michael Carome, M.D.  
Director  
Public Citizen's Health Research Group

## Tab 7b

# FDA Review of Drug Products That Employ Transdermal or Topical Delivery Systems



DATE: October 5, 2016

FROM: Caroline Strasinger, Ph.D., Office of New Drug Products, Office of Pharmaceutical Quality

THROUGH: Ashley Boam, MSBE, Acting Director, Office of Policy for Pharmaceutical Quality, Office of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Drug Products That Employ Transdermal or Topical Delivery Systems for Inclusion on the Difficult to Compound List

## I. INTRODUCTION

Drug products that employ transdermal or topical delivery systems, collectively identified as TDS, have been nominated for the list of drug products or categories of drug products that present demonstrable difficulties for compounding (the Difficult to Compound List) under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act). As discussed below, for purposes of this review, we are defining TDS to include drug products that employ matrix or reservoir type transdermal or topical delivery systems, which are designed to deliver active ingredient through the skin either systemically or locally.<sup>1</sup> Also, for the purposes of this review, FDA does not consider TDS to be liquid or semisolids, such as gels, creams, lotions, foams, ointments or sprays, that are intended for use without matrix or reservoir type transdermal or topical delivery systems (i.e., applied directly to the skin).

We have reviewed available information on the formulation, drug delivery mechanism, dosage form, bioavailability, compounding process complexity, physicochemical and/or analytical testing complexity of TDS and their likelihood to adversely affect safety or effectiveness. For the reasons discussed below, we believe the evaluation criteria weigh *in favor* of placing TDS on the Difficult to Compound List under sections 503A and 503B of the FD&C Act.

## II. BACKGROUND

### A. An Introduction to TDS

TDS are used in a range of therapeutic areas and populations, including pediatric and geriatric populations. Transdermal delivery systems are designed to deliver an active ingredient across

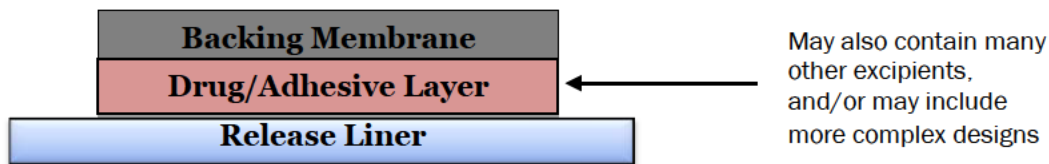
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<sup>1</sup> Where the review discusses either transdermal or topical delivery systems, but not both, the abbreviated term *TDS* is not used.

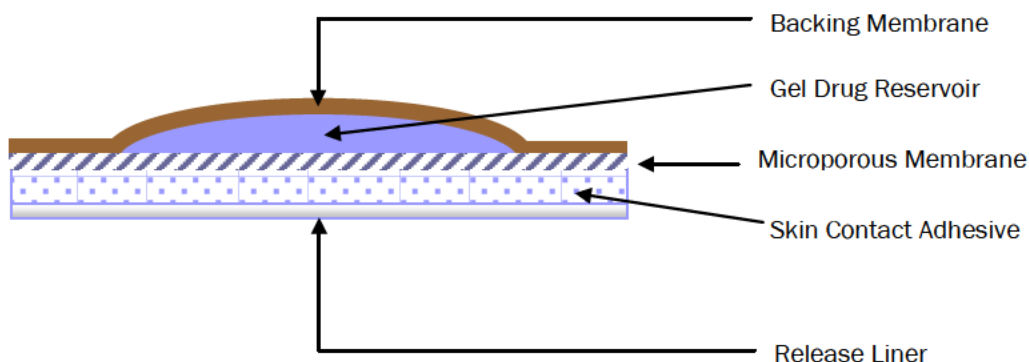
the skin and into systemic circulation, while topical delivery systems are designed to deliver the active ingredient to local tissue. Both transdermal delivery systems and topical delivery systems present similar manufacturing and quality control concerns and similar risks to patients. The types of TDS discussed in this review use matrix type or reservoir type delivery systems. Liquid and semi-solids, such as gels, creams, lotions, foams, ointments or sprays, alone, are not considered TDS for purposes of this review. Matrix type TDS contain one or more active ingredients dissolved or partially suspended in a mixture of various components, including adhesives, penetration enhancers, softeners, and preservatives and are typically manufactured using solvent, hydrogel, or hot, melt-based practices. Reservoir type TDS similarly can contain a variety of components in liquid or semi-solid form; however, reservoir type TDS that contain gels are heat-sealed between the backing membrane and a microporous membrane.

The necessary performance characteristics related to TDS include delivering active ingredients through a specific area on the skin, maintaining adequate adherence to the skin for the intended wear period, and eliciting minimal skin irritation during wear and upon removal. The necessary physical characteristics related to TDS include, at minimum, a backing membrane, an active ingredient vehicle (drug/adhesive layer or gel drug reservoir), an adhesive layer (which may or may not be part of the vehicle), and a release liner. Figures 1 and 2 depict general schematics of matrix type delivery systems and reservoir type delivery systems, respectively. If the necessary physical characteristics related to TDS are not achieved and maintained, the safety and efficacy of the product can be affected.

**Figure 1. Matrix Type Transdermal or Topical Delivery System**



**Figure 2. Reservoir Type Transdermal or Topical Delivery System**



Regardless of the physical design, the active ingredient must permeate out of the TDS and into the skin. Depending on the type of TDS, the amount of active ingredient delivered and wear time may vary significantly.

Although TDS may appear quite simple in design, they have unique characteristics that require specialized raw material selection and control, distinctive manufacturing procedures, and unique in-process and final control measures to safely and effectively deliver the desired amount of active ingredient, control impurities, maintain the required functional properties of adhesion, and limit irritation of the skin. These unique features of TDS are discussed below.

## **B. Common Examples**

Common examples of matrix type transdermal delivery systems include methylphenidate transdermal systems (e.g., Daytrana), buprenorphine transdermal systems (e.g., Butrans), and nicotine transdermal systems (e.g., Nicoderm CQ). A common example of a reservoir type transdermal delivery system is a testosterone transdermal system (e.g., Androderm).

Common examples of matrix type topical delivery systems include lidocaine 5% topical patch (e.g., Lidoderm) and menthol 3%, methyl salicylate 10% (e.g., Salonpas).

## **III. EVALUATION CRITERIA**

FDA has determined that the following criteria<sup>2</sup> should be used for evaluating whether drug products or categories of drug products present demonstrable difficulties for compounding that reasonably demonstrate, and are reasonably like to lead to, an adverse effect on the safety or effectiveness of the drug product or category of drug products:

1. Complex formulation
2. Complex drug delivery mechanism
3. Complex dosage form
4. Complex bioavailability issues
5. Complex compounding process
6. Complex physicochemical or analytical testing issues

## **IV. ANALYSIS**

### **A. TDS Have Complex Formulations**

TDS have complex formulations because they are multifaceted systems that are required to deliver active ingredients through the skin for a given therapy. TDS must provide a specified flux of active ingredient into and through the skin per unit area to achieve the desired delivery rate. Also, TDS must maintain the functional property of clinically adequate adhesion throughout the indicated wear period to provide the desired therapy. Last, TDS must be able to be worn and then removed with limited irritation to the skin. The complex characteristics of the active ingredient(s) (including polymorphic form, solubility, compatibility with other excipients, and purity) and other excipients (e.g., adhesives), as well as the batch-to-batch variability in the

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<sup>2</sup> See Tab 6 of this briefing package for more information on these criteria.

active ingredient(s) and excipients, all influence the ability of TDS to deliver the active ingredient(s) through the skin.

### *1. Active Ingredient*

Several properties of active ingredients commonly used in TDS may affect performance. These properties include, but are not limited to, the active ingredient's polymorphic form, the active ingredient's solubility in and interaction with the vehicle, the compatibility of the active ingredient and excipients, and the active ingredient's purity.

#### a. Polymorph

TDS may require the active ingredient to exist in an amorphous state or a specific polymorphic form for compatibility with the system. If an amorphous state or a specific polymorphic form of the active ingredient is important, the type and amount of polymorphic form should be limited and controlled by the manufacturing process. The influence of the storage conditions on the active ingredient and the overall compatibility of the chosen adhesive system should be evaluated as well. All of these factors have the potential to induce crystallization of the active ingredient, which could affect the amount of active ingredient available for delivery through the skin. In addition, the presence of an undesired polymorph could adversely affect the safety or efficacy of the product due to differences among polymorphs in permeation through the skin, unexpected interactions with excipients, or a decrease in product adhesion.

#### b. Solubility

In general, for transdermal or topical delivery, the active ingredient must be in a dissolved state to be delivered across the skin, and an active ingredient concentration gradient from the TDS across the skin must be maintained (i.e., sink conditions) throughout the wear period to ensure delivery of adequate therapy. The solubility of the active ingredient may vary due to a vast array of excipients, including different types (e.g., silicone, polyisobutylene, acrylic) and grades (e.g., varying monomer ratios) of adhesives, solubilizers, and cosolvents. Furthermore, an active ingredient with low solubility may pose a challenge because of difficulties in maintaining sink conditions and the active ingredient's propensity to precipitate in the TDS. Conversely, an active ingredient that is highly soluble may experience reduced release of the active ingredient from the matrix or reservoir due to the active ingredient's affinity for the vehicle.

#### c. Compatibility between the active ingredient and the excipients

Unlike tablets, where many excipients are often used as bulking agents or processing aids, active ingredient-excipient interactions in TDS are carefully crafted to formulate a product with specific quality and performance attributes. Physical, chemical, or physiological interactions between the active ingredient and excipients may affect stability, product manufacture, efficacy, performance, and therapeutic activity and may result in varying side effect profiles. For example, certain active ingredients may have an affinity to form adsorbates with crospovidone, a commonly used excipient. Although this

may be advantageous for purposes of limiting crystallization in some formulations, it can significantly affect the properties that are important to active ingredient delivery and adhesion, including molecular dispersity and the amount of water uptake into the matrix.

#### d. Purity

The purity of the active ingredient and its impurity profile are critical quality attributes that affect the safety and efficacy of a product. Rarely is the permeability of degradants or other impurities associated with TDS studied or known. Furthermore, because the influence of penetration enhancers on these impurities cannot be known without adequate studies, slight variations in chosen excipients may lead to not only greater degradation of the active ingredient, but also to enhanced delivery of impurities to the patient.

### 2. *Other Excipients*

The characterization and control of key functional excipients (e.g., adhesives) are critical to the safety, efficacy, and quality of the product. Excipients used in TDS can include various adhesives, penetration enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers/softeners, or tackifiers, all of which can influence the quality and performance attributes of the TDS. Although there are primarily three types of adhesives (acrylate, polyisobutylene, and silicone), hundreds of different adhesive grades are commercially available, each with individualized raw material characteristics (e.g., viscosity profiles, impurity profiles, solvent systems, selected crosslinkers, functional end groups), which influence the product's adhesion, active ingredient delivery, and safety profile. The performance of the product can vary widely depending on the selected adhesive.

Adequate qualification for the adhesive component of TDS often includes an assessment of the adhesive at three main stages: (1) as a raw material, (2) as a laminate (that is, in the absence of the active ingredient and other excipients), and (3) in the final product. Qualifying the adhesive as a raw material provides insight into potential differences that may exist for the same adhesive supplied by different manufacturers, by an altered manufacturing process, or even inherent batch-to-batch raw material variability from a single supplier. Examining the adhesive as a laminate can verify the functional parameters of adhesion and may also assist in identifying the impurity profiles of the adhesive. Finally, assessing the adhesive in the final product can help identify unanticipated interactions between the adhesive and other TDS excipients that might affect product performance. Once combined with an active ingredient and excipients and then dried into a film, matrices that do not exhibit the same tack, adhesion, peel, or permeation-related characteristics may result in sub-therapeutic or supra-therapeutic delivery of the active ingredient.

### **Conclusion**

TDS are complex because they must be created from ingredients with highly variable chemical and physical properties. TDS must have predictable and controllable chemical composition and physical stability and exhibit consistent functional properties of active ingredient release and adhesion, all of which can be influenced by the raw materials selected and how they are controlled. If TDS is not made correctly, taking into account the numerous properties required

of the active ingredient and the excipients, the TDS may deliver too much or too little of the active ingredient, may not adhere properly, or may cause significant skin irritation. Based on the considerations discussed above, the complexity of TDS formulations presents demonstrable difficulties for compounding.

## **B. TDS Have a Complex Drug Delivery Mechanism**

The complexity of the mechanism by which TDS deliver active ingredients through the skin presents a demonstrable difficulty for compounding. The dose delivered is affected by several factors. The qualitative and quantitative composition of the active ingredient and excipients (which influences rate of delivery), physical design of the TDS (e.g., surface area, backing membrane chosen, thickness of the adhesive matrix), and the product's ability to function (e.g., adhere) as intended all influence the delivery of active ingredient through the skin. As discussed previously, the excipients selected and their interactions with one another can significantly affect active ingredient release from the TDS and permeation through the skin to the target site, whether it is intended for systemic or local uptake. For example, for each type of adhesive (acrylate, polyisobutylene, and silicone), there are hundreds of different grades commercially available with their own unique characteristics that affect delivery and wear. Furthermore, many components in a given TDS will individually and collectively influence the rate of active ingredient delivery and product performance.

Because active ingredient delivery is proportional to the surface area of the TDS in contact with the skin, the physical design of the product also affects the therapeutic effect and safety. In addition to size, the thickness of the adhesive matrix and the type of backing membrane can influence delivery, adhesion, and stability of the TDS. For example, backing membranes with a low moisture vapor transmission rate (MVTR) could provide occlusion and thus increase the stratum corneum hydration and skin permeability, whereas backing membranes with higher MVTRs could result in different skin permeability. Other parameters, such as stiffness of the backing membrane, thickness of the drug/adhesive matrix, and size of the product, can influence skin adhesion.

## **Conclusion**

The mechanism by which an active ingredient is delivered through the skin is complex, as it involves designing and manufacturing a product that can deliver a specific amount of active ingredient per unit area per unit time, maintain adhesion for the duration of intended wear, and have minimal irritation of the skin throughout wear and upon removal. In addition, because the dose delivered is affected by several factors, lack of precise control of raw materials, the manufacturing process, and the final product would adversely affect safety and efficacy. The complexity of this drug delivery mechanism presents a demonstrable difficulty for compounding.

### **C. TDS are complex dosage forms**

TDS are complex dosage forms for the reasons discussed in sections A and B. Specifically, TDS have complex formulations, and the mechanisms by which TDS deliver active ingredient through the skin requires well-designed drug permeation parameters for predictable drug delivery. In addition, TDS must be able to maintain the functional property of adhesion throughout the duration of wear and elicit minimal irritation during wear and upon removal of the product. As mentioned in section A, various components play a critical role in the dosage form performance. With the vast array of excipients commercially available, the influence that the excipients and active ingredient have on the chemical and physical properties of each TDS manufactured is unique. Extensive product development characterizations and precise selection and control over the raw materials and the manufacturing process are essential to evaluating the drug delivery and performance characteristics of TDS. As a result, TDS are complex dosage forms that present demonstrable difficulties for compounding.

### **D. Complexity of Characterizing and Controlling Drug Bioavailability of TDS**

*Bioavailability* is defined in 21 CFR 320.1 as “the rate and extent to which the active ingredient...is absorbed from a drug product and becomes available at the site of action.” Determining bioavailability for a given TDS is difficult. TDS are complex, and small changes in performance characteristics can have a significant impact on the local and systemic bioavailability and efficacy of the product. In addition, for systemically acting TDS, several physiological factors affect the bioavailability of the active ingredient, including skin depot effects in which the epidermal, dermal, and subdermal layers can serve as a skin reservoir and cause absorption differences due to variations in the skin at the site of application throughout the body. For locally acting TDS, which may have little to no systemic uptake, bioavailability is often assessed via pharmacodynamics studies or clinical trials using endpoint approaches (e.g., pain relief).

In the context of developing TDS for FDA approval, commercial manufacturers who submit a marketing application to FDA would typically perform a multitude of in vitro, pharmacokinetic, and other in vivo assessments. There is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the product and received by the patient; yet, these measurements would be necessary to consistently make product with a delivered dose that uniformly falls within an acceptable range. Because there are no simple methods to characterize bioavailability, compounded TDS may not possess the appropriate bioavailability profile and thus could pose significant safety and efficacy risks to the patient.

### **Conclusion**

TDS are complex systems for which small changes in performance characteristics can have a significant impact upon the local and systemic bioavailability and efficacy of a product. Currently, for TDS, unlike some other dosage forms, in vitro assessments, such as in vitro release and in vitro adhesion testing, alone, are not sufficient to accurately predict permeation, bioavailability, and overall clinical effect. Therefore, bioavailability of TDS is difficult to assess and may not be achieved and it presents a demonstrable difficulty for compounding.

## **E. TDS Involve Complex Compounding Processes**

TDS require specialized processing to reproducibly yield products with predictable drug delivery and functional parameters that are critical for product performance. As shown in Figures 1 and 2, there are generally two types of TDS. Products employing reservoir type delivery systems must be heated with specialized heat sealing equipment to fully entrap the gel between the membrane layers of the product (refer to Figure 2) to prevent leaks; as such, they present difficulties for compounding. The more common matrix type delivery systems also entail use of specialized equipment and involve a complex compounding process, which is discussed in more detail below.

### *1. Mixing*

The overall unit-to-unit and batch-to-batch TDS uniformity depends on the variability of the drug/adhesive matrix itself. The matrix variability in turn depends on the variability of the active ingredient/excipient mixture that is eventually cast into a thin film. In addition to minimizing the raw material variability discussed in sections A and B, the mixing step itself is critical to achieving a uniform mixture of active ingredient and excipients.

Mixing is the primary step whereby the active ingredient and other excipients are dissolved in the drug/adhesive layer. Exceeding the solubility limit of the active ingredient or various components in the drug/adhesive layer, or incomplete mixing or dissolution of the active ingredient or other components, can result in decreased active ingredient available for delivery or variable rates in delivery. Over mixing or using excessive propeller speed during mixing can introduce air bubbles, resulting in non-uniformity of the film when cast, affecting not only adhesion, but also potentially varying the delivery rate of the active ingredient. Additionally, many TDS formulations require multiple immiscible penetration enhancers or adhesives to achieve the desired delivery and maintain proper adhesion. Variable mixing times, holds, or transfers to the next stage of processing time can lead to unintended emulsification or phase separation; thus, unit-to-unit and batch-to-batch uniformity are challenging to achieve.

### *2. Casting*

After a uniform mix is obtained, the liquid is then cast into a thin film. Although benchtop hand-held devices (e.g., doctor blades) do exist, for conventional production of the film, casting is typically performed using automated equipment with precise gap thickness and speed controls to produce uniform thickness and coat weight films. Varying thickness or coat weight directly affects total active ingredient content of the film.

In addition, most commonly, the drug adhesive mix is cast onto the release liner. Numerous release liners are commercially available with various single-sided and double-sided silicone, fluorocarbon, or fluorosilicone coatings. Choosing a release liner that is incompatible with the adhesive or casting the mix on the non-coated side of the release liner can result in permanent bonding of the release liner to the adhesive matrix, rendering the product unusable.

### 3. *Drying and Laminating*

After casting the thin film, the adhesive matrix must be dried and then the backing membrane applied to create the final bulk laminate. Appropriate drying is critical for driving off solvents, which might otherwise affect product performance, efficacy, and safety. During the drying stage, solvents and other residual impurities release into the atmosphere, leaving behind the tacky adhesive film. In conventional manufacturing, drying is performed in large multi-chamber ovens with precise control of temperatures, drying times, and airflow. Temperature profiles of the oven must often be optimized to the composition for appropriate drying. Too high of a temperature at the start of drying can drive adhesive mix solvents off too quickly, leading to bubbling in the matrix. Too low of a temperature or short drying times may not drive off enough solvent; in such cases, the matrix will be too soft or tacky for further processing or may change the active ingredient delivery rate and adhesion parameters.

From a safety perspective, the drying process is a critical step in controlling residual solvents and volatile adhesive impurities. As previously mentioned, adhesives are often solvent-based or mixed with solvents for further processing. Many raw material adhesives also contain neurotoxic, genotoxic, or mutagenic residual catalysts or impurities generated during the polymerization process. Drying processes are used to reduce these residual solvents and impurities to acceptable levels (see ICH Q3B and ICH Q3C); otherwise, they need to be controlled and the levels justified through non-clinical testing. If the critical process parameters of drying temperature, dryer air flow, and line speed are not adequately optimized and controlled, the process, efficacy, product performance, and safety may be negatively affected.

## **Conclusion**

The compounding processes for TDS are complex, and the use of specialized equipment allowing for automated processing and precise control are important for both reservoir and matrix type delivery systems. Any errors in the steps of mixing, casting, or drying of TDS are reasonably likely to result in variability in the delivered dose, product performance inconsistency, and/or unsafe levels of impurities. For the reasons discussed above, compounding TDS involves complex processes that present demonstrable difficulties.

## **F. TDS Necessitate Complex Physicochemical or Analytical Testing**

As described in more detail in this section, a large number of complex tests are needed to help ensure satisfactory performance of TDS. Furthermore, extensive characterization and developmental studies on the specific formulation, the functional properties, and the manufacturing process are necessary to develop the specifications and in-process controls that should be used to help ensure that the product has the necessary properties for delivery, safety, and performance.

### 1. *Raw Materials Testing*

As alluded to in sections A and B, rigorous qualification of adhesives, as well as other key components, is exceptionally important to the safety and effectiveness of TDS. For example, raw material properties like viscosity and impurity content often affect the quality and safety

attributes (e.g., genotoxic impurities, irritation potential) of TDS. Suppliers' adhesive specifications are often presented in quite wide ranges; thus, the properties of an adhesive raw material could vary greatly. Without establishing potentially tighter internal acceptance specifications at the manufacturing site or independently conducting complex testing of raw materials to be used, the safety and effectiveness of TDS may be adversely affected.

## *2. Release Testing*

One important release test for TDS is in vitro adhesion testing. The United States Pharmacopeia (USP) General Chapter <3>, Topical and Transdermal Drug Products, briefly highlights four in vitro adhesion tests: peel adhesion, release liner peel, tack, and shear. However, the USP does not specifically outline a precise method for each of these tests, and there are multiple methods and technical nuances to each of the tests. For example, characteristics of the method, such as the conditioning time, angle of peel, peel rate, or substrate (e.g., stainless steel) to which the product is adhered for a given test method can significantly affect the results obtained from each test. The complexity of the testing increases with the number of operators, each of which would have to achieve the same results consistently.

More importantly, the in vitro tests described do not correlate well to in vivo adhesion; rather, they can only detect gross batch-to-batch differences from a quality perspective. For a drug product to demonstrate adequate adhesion, an in vivo skin adhesion test using the proposed product should be performed during clinical development. Once the product has demonstrated adequate adhesion for the duration of wear, the in vitro adhesion tests described above may then be used to ensure the same product characteristics are maintained for each batch manufactured and throughout its shelf life. Due to the impact of and interplay among the active ingredient, adhesives, and other excipients on adhesion properties, compounded TDS would need to be tested through both in vivo and in vitro adhesion tests to ensure adequate, predictable, and reproducible adhesion for the duration of wear.

Other important release tests for TDS include assay, uniformity, impurity, and residual solvent testing. Similar to in vitro adhesion testing, sophisticated equipment and specialized methods need to be developed and used for these tests. Developing a method that can first extract particular components, like the active ingredient, from a unique adhesive matrix and then quantify the active ingredient to the preciseness of 90-110% of the total drug load of the TDS, is difficult. Furthermore, the lack of quantitation of residual monomers, adhesive impurities, and residual solvents would adversely affect the safety of the product in each batch manufactured.

## *3. Stability Testing*

TDS require both product quality and product performance testing to determine appropriate in-use periods and should be studied throughout their in-use period to help ensure that product performance is maintained during storage and administration. The effect of storage time, storage conditions, and even storage orientation (e.g., multiple products stacked flat on one another or aligned on end in a box) can affect quality and performance. The same tests used at release of the product typically need to be monitored throughout the shelf life.

With TDS, several quality concerns can arise related to stability, including stability concerns stemming from a phenomenon known as *cold flow*, crystallization of the active ingredient or other critical components, and leachables. Cold flow is the creep or oozing of the adhesive matrix beyond the perimeter of the backing membrane or through the release liner slit. The presence of excessive cold flow may cause a tacky ring around the perimeter, making it difficult for the patient to remove the TDS from the pouch and/or release liner, or result in premature product detachment or transfer to others. Crystallization, as extensively discussed above, can affect active ingredient delivery and adhesion. Chemical impurities from the backing membrane, release liner, or container closure may leach into the adhesive matrix or reservoir due to residual solvents. Because the toxicity and skin penetration potential is unknown for many of these unknown leachates, leachable and extractable studies are typically performed during development of a product, and appropriate limits set when identified.

Finally, penetration enhancers are often volatile chemicals in the formulation. If the concentration of the penetration enhancer is not maintained during storage, then an impact on the delivery rate can be expected, whether it is an increase in time to reach steady state or the lack of maintaining the desired steady state once reached. Furthermore, if penetration enhancers are only marginally compatible with the adhesive, there could be a change in physical properties that could affect function or use, such as adhesion or appearance.

## **Conclusion**

TDS require complex physicochemical and analytical testing (including raw material, release, and stability testing) because the physical and chemical properties of the raw materials and finished product as well as product-critical performance parameters require complex analytical devices and procedures for accurate measurement. Furthermore, chemical impurities from both the degradation of the active ingredient and adhesives, and those that can be leached from the backing membrane, release liner and container closure components must be quantitated through various sensitive analytical techniques developed specifically for these impurities. The physicochemical and analytical testing required for TDS are so complex that they present demonstrable difficulties for compounding.

## **V. RISKS AND BENEFITS TO PATIENTS**

TDS have grown in popularity since their introduction in 1979. Currently, there are approximately 25 unique TDS on the market, many available with generic formulations, all approved under a new drug application or abbreviated new drug application submitted to FDA. These products are currently considered an indispensable treatment for a variety of diseases and ailments, and for preventative therapy. Examples of uses for these products include the management of severe pain, treatment of the symptoms of Parkinson's and Alzheimer's diseases, nicotine replacement for smoking cessation, and birth control.

As discussed above, the relationship of the various excipients with the active ingredient and with each other directly affect not only drug delivery, but product performance and safety. Although some ingredients in approved TDS may cause hypersensitivity, such as contact dermatitis, an

attempt to compound TDS by replacing specific ingredients in an approved TDS with other ingredients that perhaps may not cause hypersensitivity is reasonably likely to adversely affect product performance. The most common ingredients known to cause irritation include the active ingredient, adhesives, and penetration enhancers. The active ingredient cannot be avoided, and attempting to substitute or remove an adhesive or penetration enhancer would likely change the delivery and performance characteristics of a product, adversely affecting its safety and efficacy. Also, strict quality controls on raw materials, the manufacturing process, and the product are essential to manufacturing products of predictable and reproducible drug delivery, performance, and safety profiles. Any benefit of allowing these products to be compounded is outweighed by the risks discussed above.

## **Conclusion**

TDS are complex systems that can be effective and safe when the product has the proper formulation and dosage form, the drug delivery mechanism is designed correctly, appropriate bioavailability is assessed and achieved, the proper manufacturing process is employed, and the necessary physicochemical and analytical tests are performed. The significant risks posed by TDS that do not possess all these characteristics outweigh the benefits of allowing these products to be compounded.

## **VI. RECOMMENDATION**

We have evaluated the category of TDS as a candidate for the Difficult to Compound List. Based on an analysis of the evaluation criteria, we believe that TDS present demonstrable difficulties for compounding that reasonably demonstrate, and are reasonably like to lead to, an adverse effect on the safety or effectiveness of this category of drugs, taking into account the risks and benefits to patients. Accordingly, we believe TDS should be included in the Difficult to Compound List under sections 503A and 503B of the FD&C Act.

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