CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

89-202

Generic Name:	Folic Acid Injection USP, 5mg/mL 10mL Vials
Sponsor:	LyphoMed, Inc.
Approval Date:	February 18, 1986

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

APPROVAL LETTER

ANDA 89-202

FEB 18 1986

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illionis 60160

Dear Madam:

Reference is made to your abbreviated new drug application dated May 22, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection USP, 5 mg/mL, 10 mL Vials.

Reference is also made to your communications dated December 27, 1985 and February 11, 1986.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the New Drug Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This Administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253.

Sincerely yours,

Marvin Seife 2/18/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO
HFN-83
HFN-230
HFN-10
KJohnson/JMeyer/LValenti
R/D INITIALED BY: JMeyer/MSeife
D Utz: 2-13-86 (0326R)
APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

FINAL PRINTED LABELING

10/185

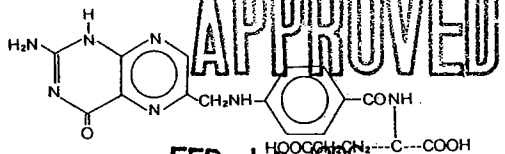
LyphoMed®

FOLIC ACID INJECTION, USP

For Parenteral Use

DESCRIPTION:
Folic Acid Injection, USP is a sterile, nonpyrogenic solution of folic acid in Water for Injection intended for intramuscular, intravenous or subcutaneous use.

Folic Acid is a complex organic compound present in liver, yeast and other substances, which may be prepared synthetically. It is a yellow or yellowish orange, odorless crystalline powder. It is very slightly soluble in water, insoluble in alcohol, chloroform, ether; readily dissolves in dilute solutions of alkali hydroxides and carbonates. It is chemically designated as: L-Glutamic acid, *N*-[4-[[(2-amino-1-4-dihydro-4-oxo-6-pteridinyl) methyl]amino]benzoyl]-, and has the following structural formula.



APPROVED
FEB 18 1986

$C_{19}H_{19}N_7O_6$ 441.40

Each mL contains: Folic acid 5 mg; Edetate disodium 2 mg; Benzyl alcohol 15 mg; and Water for Injection, q.s. Sodium hydroxide and/or hydrochloric acid to adjust pH between 8.0 and 11.0.

CLINICAL PHARMACOLOGY:
In man, an exogenous source of folate is required for nucleoprotein synthesis and maintenance of normal erythropoiesis. Folic acid, whether given by mouth or parenterally, stimulates specifically the production of red blood cells, white blood cells, and platelets in persons suffering from certain megaloblastic anemias.

INDICATIONS:
Folic acid alone is effective in the treatment of megaloblastic anemias due to a deficiency of Folic Acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS:
Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where Vitamin B_{12} is deficient.

PRECAUTIONS:
Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive.

ADVERSE REACTIONS:
Allergic sensitization has been reported following both oral and parenteral administration of Folic Acid.

DOSAGE AND ADMINISTRATION:
Parenteral Administration: Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe or if gastrointestinal absorption may be, or is known to be, impaired.

Usual Therapeutic Dosage—In adults and children (regardless of age): up to 1.0 mg daily. Resistant cases may require larger doses.

Maintenance Level: When clinical symptoms have subsided and the blood picture has become normal, a maintenance level should be used, i.e., 0.1 mg for infants and up to 0.3 mg for children under four years of age, 0.4 mg for adults and children four or more years of age, and 0.8 mg for pregnant and lactating women, per day, but never less than 0.1 mg per day. Patient should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

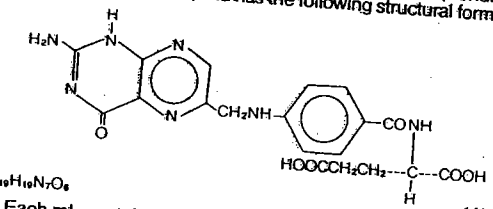
LyphoMed®

FOLIC ACID INJECTION, USP

For Parenteral Use

DESCRIPTION:
Folic Acid Injection, USP is a sterile, nonpyrogenic solution of folic acid in Water for Injection intended for intramuscular, intravenous or subcutaneous use.

Folic Acid is a complex organic compound present in liver, yeast and other substances, which may be prepared synthetically. It is a yellow or yellowish orange, odorless crystalline powder. It is very slightly soluble in water, insoluble in alcohol, chloroform, ether; readily dissolves in dilute solutions of alkali hydroxides and carbonates. It is chemically designated as: L-Glutamic acid, *N*-[4-[[(2-amino-1-4-dihydro-4-oxo-6-pteridinyl) methyl]amino]benzoyl]-, and has the following structural formula.



$C_{19}H_{19}N_7O_6$ 441.40

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

W SUPPLIED:
ic Acid Injection (5 mg/mL) is available as:

duct No.	NDC No.	
184-10	0469-1840-30	10 mL Multiple Dose, flip-top vials packaged individually.

ore at controlled room temperature 15°-30°C (59°-86°F).
otect from light. Retain vial in box until contents are used.

AUTION:
ederal (USA) law prohibits dispensing without prescription.

FEB 18 1986

APPROVED

LyphoMed, Inc.
Melrose Park, IL 60160

06-03-0501
Issued or Revised: July 1985

HOW SUPPLIED:
Folic Acid Injection (5 mg/mL) is available as:

Product No.	NDC No.	
184-10	0469-1840-30	10 mL Multiple Dose, flip-top vials packaged individually.

Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light. Retain vial in box until contents are used.

CAUTION:
Federal (USA) law prohibits dispensing without prescription.

LyphoMed, Inc.
Melrose Park, IL 60160

06-03-0501
Issued or Revised: July 1985

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING

ANDA - DRAFT

DATE OF REVIEW: 6/22/85

ANDA #: 89-202 NAME OF FIRM: LyphoMed

NAME OF DRUG: Generic: Folic Acid Injection USP

DATE OF SUBMISSION: 5/22/85

COMMENTS:

Container: Not Satisfactory
A. Edetate disodium . . . . (rather than ~~———~~
B. following; Protect from light, add, Retain vial in carton until contents are used. (see USP XXI, Suppl 2)

Insert: Not Satisfactory
A. DESCRIPTION:
1. Chemist: Comment on chemical name. We generally ask for the name noted in the USP.
2. Edetate disodium is established name.

B. HOW SUPPLIED:
1. . . . . controlled room temperature

RECOMMENDATIONS:

1. Inform firm of the above comments.

2. Request that they revise labels and labeling, then prepare and submit FPL.

Kent T. Johnson

cc: Dup.
KJohnson/mk/6/24/85
0234m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW NDA 89-202

3. NAME AND ADDRESS OF APPLICANT
LyphoMed Inc
2020 Ruby Street
Melrose Park, IL Attention: Diane M. Komos

6. NAME OF DRUG
Folic Acid Injection

7. NONPROPRIETARY NAME
None

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Original

10. PHARMACOLOGICAL CATEGORY
Hematopietic Vitamin

11. HOW DISPENSED
Rx

13. DOSAGE FORM(s)
Injection

14. POTENCY
5 mg/ml

17. COMMENTS
Deficient

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved

19. REVIEWER:
Len Valenti

DATE COMPLETED:
7/8/85

APPEARS THIS WAY
ON ORIGINAL

20. COMPONENTS AND COMPOSITION
    6. Satisfactory
    7. Does not contain [redacted]

21. FACILITIES AND PERSONNEL
    Facilities not described

22. SYNTHESIS
    [redacted] No referral letter

23. RAW MATERIAL CONTROLS
    A. NEW DRUG SUBSTANCE: Firm to include a test for " [redacted]
    8e. Numbering System for raw materials satisfactory

    B. OTHER INGREDIENTS:
    Firm to submit Certificate of Analysis for inactive ingredients.

24. OTHER FIRM(s)
    [redacted]

25. MANUFACTURING AND PROCESSING
    8g. Satisfactory
    8h. Satisfactory
    8J. Satisfactory
    8K. Satisfactory but firm to submit additional information on filling

26. CONTAINER
    Satisfactory

27. PACKAGING AND LABELING
    Insufficient information on packaging

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)
Satisfactory

29. STABILITY
Satisfactory
Request 2 years

30. CONTROL NUMBERS
Satisfactory

31. SAMPLES AND RESULTS
Samples sent to St. Louis
Samples sent to Chicago Aug 6, 1985
32. LABELING
Not Satisfactory See comments K. Johnson 6-22-85

33. ESTABLISHMENT INSPECTION
Establishment Evaluation Requested May 29, 1985

34. RECALLS
N/A

APPEARS THIS WAY
ON ORIGINAL

CHEMIST REVIEW 89-202

NAME AND ADDRESS OF APPLICANT
LyphoMed Inc.
2020 Ruby Street
Melrose Park, Illinois

PURPOSE OF AMENDMENT
Resubmission - NDA Original amendment

PHARMACOLOGICAL CATEGORY
Hemalopieptic Vitamin

NAME OF DRUG
Folic Acid

DOSAGE FORM:
Injection

POTENCY
5 mg/mL 10 mL Vial

DATE OF SUBMISSION
July 24, 1985

HOW DISPENSED
Rx

STERILIZATION
Satisfactory

SAMPLES
Waiting for results from St. Louis and Chicago

satisfactory

LABELING
Waiting for FPL

BIOLOGIC AVAILABILITY
Waiver requested for in-vivo study granted August 14, 1985

ESTABLISHMENT INSPECTION
Waiting for review

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROL
Not Satisfactory - Manufacturing SOP's not given controls. Updated to the current compendium.

PACKAGING
Vials - Type I Glass - [redacted] USP tested 10 mL

STABILITY
Procotol: Satisfactory
Exp. Date: 18 months

REMARKS AND CONCLUSIONS
Not Approved

REVIEWER
Len Valenti

DATE
8/19/85

Len Valenti

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

89-202

NAME AND ADDRESS OF APPLICANT

phoMed
2020 Ruby Street
Melrose Park, Illinois

ORIGINAL
AMENDMENT XX
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

FPL Labeling

DATE(S) OF SUBMIS

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
hematopoietic Vitamin	Folic Acid	RX XX OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/I
Parenteral 10 ml Vial	5 mg/ml, 10 ml Vial	
CERTIFICATION	SAMPLES Assigned St. Louis - Sample - Satisfactory Chicago - Waiting for Results	

LABELING

Final Printed Carton/Container labels and insert are satisfactory. Kent Johnson 8/26/85

BIOLOGIC AVAILABILITY

The firm has met the in-vivo bioequivalence requirement. August 14, 1985 Bioeq.

ESTABLISHMENT INSPECTION

Currently under Review by the field 9/5/85

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Letter sent Aug. 20, 1985 listing deficiencies.

PACKAGING

Vial Type I Glass _____ USP tested 10 ml _____
supplied by _____

STABILITY

Protocol: Satisfactory - 3 month stability satisfactory

Exp. Date: 18 month

REMARKS AND CONCLUSIONS: Not Approved - pending - Satisfactory EIR and GMP's
Results from Chicago, and deficiencies listed in Aug. 20, 1985 letter.

Leonard Valenti Leonard Valenti 9/9/85

CHEMIST REVIEW 89-202

NAME AND ADDRESS OF APPLICANT
LyphoMed Inc.
Melrose Park, IL

PURPOSE OF AMENDMENT/SUPPLEMENT
Resubmission

HOW DISPENSED
Rx

PHARMACOLOGICAL CATEGORY
Vitamin

NAME OF DRUG
Folic Acid

DOSAGE FORM
Injection (10 mL Vial)

POTENCY
5 mg/mL

STERILIZATION
Satisfactory

SAMPLES
Satisfactory August 23, 1985
Product - Assign to CHI-DO August 6, 1985.

LABELING
FPL container labels carton and insert satisfactory Kent Johnson August 26, 1985.

BIOLOGIC AVAILABILTY
Waiver requested for in-vivo study granted August 14, 1985

ESTABLISHMENT INSPECTION
Waiting for HFN-322 Review.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
Not Satisfactory - inactive ingredient Not USP grade

PACKAGING
Vials Type I Glass ——— USP test

STABILITY
Protocol: Satisfactory
Exp. Date: 18 months

REMARKS AND CONCLUSIONS
Not Approved

REVIEWER
Len Valenti

DATE
9/25/85

CHEMIST REVIEW 89-202

NAME AND ADDRESS OF APPLICANT
LyphoMed, Inc.
Melrose Park, Illinois

PURPOSE OF AMENDMENT/SUPPLEMENT
Resubmission October 7, 1985

PHARMACOLOGICAL CATEGORY
Vitamin

NAME OF DRUG
Folic Acid

DOSAGE FORM
10 mL Vial Injection

POTENCY
5 mg/mL

SAMPLES
Bulk drug samples St. Louis - Satisfactory

HOW DISPENSED
Rx

LABELING
FPL containers and insert labeling satisfactory

BIOLOGIC AVAILABILITY
In-vivo waiver granted August 14, 1985

ESTABLISHMENT INSPECTION
Approvable August 23, 1985 and October 10, 1985

COMPOSITION, MANUFACTURING, COMPONENTS, CONTROLS
All components, USP grade
Manufacturing and controls - Satisfactory

PACKAGING
Vials Type I Glass supplied by [redacted]

STABILITY
Protocol: Not Satisfactory firm to be performed
Exp. Date: 18 months

REMARKS AND CONCLUSIONS
Not Approved

REVIEWER
Len Valenti

DATE
11/22/85

CHEMIST REVIEW 89-202

NAME AND ADDRESS OF APPLICANT
LyphoMed, Inc.
Melrose Park, Illinois

PURPOSE OF AMENDMENT
To inform comments of sample analysis

PHARMACOLOGICAL CATEGORY
Megaloblablastic Anemis

NAME OF DRUG
Folic Acid

DOSAGE FORM
Injection 10 mL Vial

POTENCY
5 mg/mL

STERILIZATION
Satisfactory

SAMPLES
Sample Results - raw material
Satisfactory - St. Louis
Drug Product - [redacted]
firm to submit sample results.

HOW DISPENSED
Rx

LABELING
Final Printed Labeling Satisfactory

ESTABLISHMENT INSPECTION
GMP's Approvable October 10, 1985

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
All components listed
Composition Satisfactory
Manufacturing described satisfactory
Master Formula - OK
Controls tested as per USP XXI

PACKAGING
10 mL Glass Vials - [redacted] USP Tested

STABILITY
Protocol: Satisfactory
Exp. Date: 18 months

REMARKS AND CONCLUSIONS
Not Approved
Firm to comment on [redacted] Test

REVIEWER
Len Valenti

DATE
12/18/85

Len Valenti

CHEMIST REVIEW 89-202
STATEMENT DATE: December 27, 1985

NAME AND ADDRESS OF APPLICANT
LyphoMed
Melrose Park, Illionis

PURPOSE OF AMENDMENT/SUPPLEMENT
Test results data from firm for [redacted], test

PHARMACEUTICAL CATEGORY
Hemapoetic Vitamin

NAME OF DRUG
Folic Acid

DOSAGE FORM
Injection 10 mL Vial

POTENCY
5 mg/mL

DATE OF SUBMISSION
May 22, 1985

SUPPLEMENT
N/A

STERILIZATION
Satisfactory

SAMPLES
[redacted]
Satisfactory August 23, 1985
[redacted] - Results satisfactory [redacted]
[redacted] Adequately answered.

LABELING
Final printed labeling Satisfactory and printed Insert labeling - Satisfactory Kent Johnson August 26, 1985.

BIOLOGIC AVILABILITY
In-vivo waiver granted August 14, 1985

ESTABLISHMENT INSPECTION: Granted August 14, 1985

ESTABLISHMENT INSPECTION
Approved October 10, 1985 T. Bozzo HFN-322

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
All components listed as USP grade
Master Formula - OK
Composition - All Satisfactory
Control Test - Satisfactory

PACKAGING
10 mL Vials Type I glass supplied by [redacted] - USP tested
[redacted]

STABILITY
Protocol: Satisfactory 3 month accelerated stability satisfactory
Exp. Date: 18 month expiration date

REMARKS AND CONCLUSIONS
Approve Firms results for [redacted] test satisfactory

REVIEWER
Len Valenti

DATE
2/13/86

Len Valenti

— Valbati

******* SAMPLE ANALYSIS REPORT *******
DIVISION OF DRUG ANALYSIS
CENTER FOR DRUGS AND BIOLOGICS
FOOD AND DRUG ADMINISTRATION
SAINT LOUIS, MISSOURI

LABORATORY CONCLUSIONS Meets USP XXI, DP — SUPERVISOR'S INITIALS
DISTRICT CONCLUSIONS NAS — [illegible]

STUDY# 052 ANDA DRUGS — SAMPLE# 89-202-000

PRODUCT: FOLIC ACI — 100.00 % ACTIVE DRUG SUBSTANCE
MANUFACTURER: LYPHOM — MELROS — IL — BATCH# &M42359
ANALYZED FOR: FOLIC ACID — (A) — RECEIVED 7-11-85
METHOD OF ANALYSIS:
1. QUALITATIVE:
2. DISINTEGRATION: NA
3. QUANTITATIVE: USP XXI PG449 — METHOD CODE: 3A
LIMITS: USP XXI
STRENGTH: ——— OF DECLARED AMOUNT

BATCH RESULTS

	AVE%	NO. OUT	LOW HIGH	R.S.D.%
SUB#	--- % OF LABEL DECLARATION ---			
1	—	0	—	*****

ANALYST: 587 PC:3 JAMES F. ALLGIRE James Allgire
REPORTING DATE: 8-23-85

OPERATION: 41 HOME DIST: — HRS: 1 METHOD: CHEM
TOTAL REPORTED EXAMINATIONS... 6 ..... PAC 56008A
EXPIRATION DATE: .....
NATIONAL DRUG CODE: — DRUG REGISTRATION NUMBER: —

DATE 8-23-85 CALC. CHECK ..... PAGE 1 OF 4 PAGES
COMPUTERIZED WORKSHEET USED FOR DATA PRESENTATION

Manufacturer: ———

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

BIOEQUIVALENCE REVIEW(S)

AUG 5 1985

Folic Acid Injection, USP
5 mg/ml - 10 ml vial
ANDA #89-202
Reviewer: Beatrice Chen
Wang #5670e

LyphoMed, Inc.
Melrose Park, Ill.
Submission Date:
May 22, 1985

REVIEW OF A REQUEST FOR A WAIVER OF AN IN-VIVO BIOEQUIVALENCE STUDY

Objective:

The firm is requesting a waiver of bioequivalence testing for Folic Acid Injection, USP under CFR 320.22 (b)(1)(i)(ii) which requires that the product be (i) a solution intended solely for intravenous administration, and (ii) it contains an active drug ingredient in the same solvent and concentration as an intravenous solution of an approved application.

Background:

1. The injection product is intended for intramuscular, intravenous or subcutaneous use. The regulation on such parenteral drug product should be according to CFR 320.22 (c)(2) that both active and inactive ingredients be identical to an approved drug product - FOLVITE^{R}.

2. The full composition of the injection product and FOLVITE^{R} is as follows:

per ml of solution	Folic Acid Injection, USP (LyphoMed)	FOLVITE^{R} (Lederle)
Folic Acid, USP	5.0 mg	5 mg
Disodium EDTA Reagent Grade	2.0 mg	0.2% (2 mg)
Benzyl Alcohol, NF	15.0 mg	1.5% (15 mg)
Water for Injection, USP	q.s. to 1 ml	q.s. to 100%
Sodium Hydroxide, NF (— to adjust pH	8.0 - 11.0	8.7 - 9.3
Hydrochloric Acid, NF (— to adjust pH		

Comment:

1. All components are identical except the pH range of the drug being 8.0 to 11.0 which is wider than that (pH 8.7 to 9.3) of the approved drug FOLVITE^{R}.

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

The Division of Bioequivalence agrees that the information submitted by LyphoMed, Inc. demonstrates that Folic Acid Injection, USP, 5 mg/ml falls under 21 CFR Section 320.22 (c)(2) of Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioequivalence be granted for folic acid injection, 5 mg/ml (10 ml vial). From the bioequivalence point of view, the firm has met the in-vivo bioequivalence requirement and the test injectable formulation is deemed to be bioequivalent to Folvite, 5 mg/ml (10 ml) manufactured by Lederle Laboratories.

Beatrice Chen

Beatrice Chen, Ph.D.
Division of Bioequivalence
Review Branch 1

RD INITIALED CISE C. M Lee
FT INITIALED CISE

BChen/cc/7-11-85/Wang # 5670e

cc: ANDA # 89-202 original, HFN-230, HFN-200 (Hare), HFN-223 (Shah - 2), HFN-252 (Ise, BChen), Drug File

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

ADMINISTRATIVE DOCUMENTS

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER 89-202

DATE APPROVAL LETTER ISSUED FEB 18 1986

TO: Press Relations Staff (HFI-40)

FROM: [X] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [X] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [X] HUMAN [ ] VETERINA

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG

Folic Acid Injection

ORIGINAL ABBREVIATED

DOSAGE FORM: Injection 10 mL Vial

HOW DISPENSED: [X] RX [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Folic Acid USP 5 mg/mL

APPEARS THIS WAY ON ORIGINAL

NAME OF APPLICANT (Include City and State)

LyphoMed, Inc.
2020 Ruby Street
Melrose Park, Illionis

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Hematopoietic Vitamin

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: L. Valenti DATE:

FORM APPROVED BY

NAME: J. Meyer DATE:

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: 5/29/85
Division of Drug Quality Compliance

FROM :Division of Generic Drugs
Requester's Name Diane F. Walker PHONE: 443-4080

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 89-202

DRUG TRADE MARK (if any) _____

DRUG NONPROPRIETARY NAME: Folic Acid Injection USP, 5 mg/ml, 10 ml vial

DOSAGE FORM AND STRENGTH(S): SVP

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) _____ A or B _____ 1C _____ Other _____ _____

APPLICANT'S NAME: LyphoMed, Inc.
ADDRESS: 2020 Ruby St., Melrose Park, ILL

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

1. applicant - mfr finished dosage form, dmf
2.
3.
4.

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: _____

****

FOR HFN-322 USE ONLY:

Request Rec'd: _____ Inspection Requested: _____
(if applicable)

Firm(s) are in Compliance With GMPs: Approved
Basis for Decision:
Reviewing CSO: FRT 8/23/85 Concurrance: Ronn Bopp
FRT 10-10-85

cc: HFN-____
HFN-____
HFN-322

FORM FDA 3274 (1/83)

JUN 6 1985

cc: HFC-131 D. Darrow

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date · August 6, 1985

From Scientific Coordinator
Drugs, Devices and Radiological Health Branch (HFC-142)

Subject Method Validation Assignment - 89-202 Folic Acid
FIRM: Lyphomed, Chicago, Illinois

To Len Valenti (HFN-233)

ANDA 89-202 has been assigned to the Chicago District laboratory (HFR-5160) for validation. Please instruct the firm to send the samples, methods, and standards necessary for the analyses to the laboratory as soon as possible.

Thank you for your cooperation.

Stephen Sherber Jr.
Salvatore J. Pinella

cc: Joe Brucciani (HFR-5160)
Jack Meyer (HFN-233) ✓

APPEARS THIS WAY
ON ORIGINAL

UNITED STATES GOVERNMENT

memorandum

DATE: November 27, 1985

REPLY TO ATTN OF: Chemist, CHI-DO Laboratory Facility, HFR-5160

SUBJECT: Telephone Conversations Re: ANDA's 89-202 and 88-939

TO: Sal Pinella, Scientific Coordinator, DFS, HFC-142
THRU: M. Catherine L. Chung, Supervisory Chemist, HFR-5160 MCLC

The status of LyphoMed ANDA 89-202, Folic Acid Injection; and specifications and test procedures to be used in validating LyphoMed ANDA 88-939, Leucovorin Calcium for Injection were discussed in a telephone conversation between John Marchin, Chemist, CHI-DO and Salvatore Pinella, Scientific Coordinator, DFS on 11/14/85.

The status of ANDA 89-202, Folic Acid Injection was reported to be complete as 1/13/85. It was noted in the conversation that the product failed the _____ test specification. The applicability of this test to the product was discussed and is further detailed in the memo and comments which will accompany the submission of the validation study. Also noted in the conversation was the lack of commercially labeled products for testing (copy of label submitted). Also discussed were changes in specifications and test methods between those submitted by the NDE Chemist and those submitted by the manufacturer with the samples. In particular, the omission of the _____ test specification from the manufacturers submission and no analytical data submitted to indicate that the test was performed by the manufacturer on this lot of product. I was instructed that Mr. Leonard Valenti, NDE Chemist would contact me for further discussion of the validation results.

In discussing the tests for ANDA 88-939, Leucovorin Calcium for Injection, it was again noted that the products supplied were not commercially labeled (copy submitted); and the assay procedure sent with the assignment from the NDE Chemist was in this case significantly different from that sent by the manufacturer (LyphoMed) with the sample. Both are HPLC procedures; however, the _____ are different. The _____ is different. Also discussed was the requested performance of the test for particulate matter in _____ The method is not specified but is assumed to be USP XXI, p. 1257. This test requires instrumentation and presumably expertise which is not available in our laboratory. Additionally, this test and specification is not included in the procedure sent by the manufacturer with the sample. The test and specification for clarity and completeness of solution is also omitted in the submission by the manufacturer. The requested test for the _____

OPTIONAL FORM NO. 10
(REV. 1-80)
GSA FPMR (41 CFR) 101-11.6
5010-114

☆ GPO : 1981 O - 341-526 (6587)

assay for the Leucovorin Calcium Injection was also discussed. The [redacted] determination is based on a [redacted] using an [redacted] The procedure is written as instructions for the use of this particular piece of equipment. We do not have this piece of equipment or any similar piece of equipment and therefore cannot perform the requested test. Tests and procedures written for a particular piece of equipment are not suitable for regulatory use.

As requested, I am sending copies of the procedures sent by the NDE Chemist with Form FD 2871(a) for ANDA 88-939; and also a copy of the letter and Exhibits A and B which were sent with the sample by LyphoMed. I am omitting Exhibits C and D.

As instructed no work will begin on ANDA 88-939 until problems have been corrected and we are notified.

When work begins please note that the [redacted]

On 11/15/85, Mr. Leonard Valenti; NDE Chemist for ANDA 89-202, Folic Acid Injection called as was anticipated. Topics regarding the validation were discussed. No additional work was requested. The validation study with comments will be submitted as soon as possible.

[redacted] the subject drug [redacted] 2 weeks, please [redacted]

John Marchin
JOHN MARCHIN

[redacted] you have any questions or problems, or if the requested [redacted] cannot be met, please advise Mr. Salvatore Pinella [redacted] the undersigned.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

(Division Director)

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date • December 12, 1985

From Scientific Coordinator
Drugs, Devices and Radiological Health Branch (HFC-142)

Subject Methods Validation Report: ANDA 89-202 - Folic Acid Injection
FIRM: LyphoMed, Melrose Park, Illinois 60160

To Jack Meyer
Supervisory Chemist
Division of Generic Drug Monographs
ANDA Review Branch I (HFN-233)

Through: W. Michael Rogers
Director
Drugs, Devices and Radiological Health Branch (HFC-142)

The Chicago District laboratory has completed their USP XXI testing of the subject drug product and find the analytical results meet with the USP XXI specifications.

In addition, CHI-DO validated the firm's benzyl alcohol procedure and a _____ test. The benzyl alcohol procedure is suitable for regulatory purposes as modified by CHI-DO laboratory and the results generated for _____ failed to meet the specified limits set forth in the ANDA.

All pertinent information regarding analytical testing and the laboratory's observations/ comments can be found in the attached report.

If you have any questions or need any clarification on some tests, please let me know.

Salvatore J. Pinella
Salvatore J. Pinella

Attachment

cc: Joseph Brucciani (HFR-5160)
Marvin Seife, M.D. (HFN-230)
Len Valenti (HFN-233)

Dated: October 7, 1980.

Sa A. Miller,

Director, Bureau of Foods.

[FR Doc. 80-32280 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 80F-0401]

Eastman Chemicals Division, Eastman Kodak Co.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: Eastman Chemicals Division, Eastman Kodak Co. has filed a petition proposing that the food additive regulations be amended to broaden the mole percentages of ethylene glycol and 1,4-cyclohexane dimethanol to 99–66 and 1–34, respectively, in the mixture used as a reactant with dimethyl terephthalate in the production of ethylene-1,4-cyclohexylene dimethylene terephthalate copolymer intended for food-contact use.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St., SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348)) notice is given that a petition (FAP 0B3523) has been filed by Eastman Chemicals Division, Eastman Kodak Co., Kingsport, TN 37662, proposing that § 177.1315 *Ethylene—1,4-cyclohexylene dimethylene terephthalate copolymer* (21 CFR 177.1315) be amended to broaden the mole percentages of ethylene glycol and 1,4-cyclohexane dimethanol to 99–66 and 1–34, respectively, in the mixture used as a reactant with dimethyl terephthalate in the production of ethylene-1,4-cyclohexylene dimethylene terephthalate copolymer intended for food-contact use.

FDA has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting the document may be seen in the office of the Hearing Clerk (HFA-[illegible]ood and Drug Administration, Rm. 4-[illegible]5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 7, 1980.

Sanford A. Miller,

Director, Bureau of Foods.

[FR Doc. 80-32289 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

Farmland Industries, Inc.; Co-op Chick Fortifier; Withdrawal of Approval of NADA

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency withdraws approval of a new animal drug application (NADA) providing for use of Co-op Chick Fortifier (amprolium) premix. Finished feeds containing the premix are fed to poultry as an aid in prevention of coccidiosis or for development of immunity to coccidiosis. The sponsor, Farmland Industries, Inc., requested the withdrawal of approval.

EFFECTIVE DATE: October 27, 1980.

FOR FURTHER INFORMATION CONTACT: Vitolis E. Vengris, Bureau of Veterinary Medicine (HFV–214), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3183.

SUPPLEMENTARY INFORMATION: Farmland Industries, Inc., P.O. Box 7305, Kansas City, MO 64116, is the sponsor of NADA 44–364 which provided for use of Co-op Chick Fortifier (0.50 percent amprolium) premix in making finished poultry feeds. The feeds are indicated as aids in prevention of coccidiosis in broiler chickens, turkeys, and laying hens or for development of active immunity to coccidiosis in replacement chickens under conditions of slight exposure to coccidiosis. The application was originally approved November 10, 1970. By letter of April 22, 1980, the sponsor requested withdrawal of approval of the NADA because the product is no longer being manufactured or marketed.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(e), 82 Stat. 345–347 (21 U.S.C. 360b(e))), under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.84), and in accordance with § 514.115 *Withdrawal of approval of applications* (21 CFR 514.115), notice is given that approval of NADA 44–364 and all supplements for Farmland Industries, Inc., Co-op Chick Fortifier is hereby withdrawn, effective October 27, 1980.

Dated: October 8, 1980.

Gerald B. Guest,

Acting Director, Bureau of Veterinary Medicine.

[FR Doc. 80-32118 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

[DESI 5897; Docket No. 80N-0379]

Folic Acid Preparations, Oral and Parenteral for Therapeutic Use; Drugs for Human Use; Drug Efficacy Study Implementation; Amendment

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice amends a previous **Federal Register** notice for folic acid by revising the Precautions statement to be included in the labeling for these drugs. The agency believes the revised labeling more accurately states the level at which folic acid may obscure pernicious anemia.

DATE: Supplements to approved NDA's and ANDA's due on or before December 16, 1980.

ADDRESS: Communications in response to this notice should be identified with the reference number DESI 5897, directed to the attention of the appropriate office named below, and addressed top the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Supplements to full new drug applications (identify with NDA number): Division of Metabolism and Endocrine Drug Products (HFD–130), Rm. 14B–03, Bureau of Drugs.

Original abbreviated new drug applications or supplements thereto (identify as such): Division of Generic Drug Monographs (HFD–530), Bureau of Drugs.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD–310), Bureau of Drugs.

FOR FURTHER INFORMATION CONTACT: David T. Read, Bureau of Drugs (HFD–32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3650.

SUPPLEMENTARY INFORMATION: A notice published in the **Federal Register** of April 9, 1971 (36 FR 6843), announced the conditions under which the FDA would approve new drug applications for folic acid preparations. The labeling conditions included the following precaution:

> Folic acid especially in doses abaove 1.0 mg daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

This same precaution was required in an amendment published August 2, 1973 (38 FR 20750).

Based on available data and information the Director of the Bureau of Drugs finds that the precautions section of the labeling conditions for folic acid preparations should be amended. While obscuration of pernicious anemia does not ocur at levels of 0.1 mg for folate per day, hemotologic remissions in pernicious anemia have been reported at levels as low as 0.25 mg of folate per day. The precautions section of the labeling conditions for folic acid preparations is amended to read as follows:

Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive.

Supplements to approved NDA's or ANDA's providing for appropriate revision of the labeling of drug products affected by this notice should be submitted on or before December 16, 1980. The revised labeling may be put into use before FDA approves the supplemental NDA or ANDA, but it shall be put into use no later than February 17, 1981.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)), and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82).

Dated: October 6, 1980.

J. Richard Crout,

Director, Bureau of Drugs.

[FR Doc. 80-32293 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

Jensen-Salsbery Laboratories; Anthelin Tablets; Withdrawal of Approval of NADA

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) withdraws approval of a new animal drug application (NADA) providing for use of anthelin tablets as an anthelmintic in dogs. The sponsor, Jensen-Salsbery Laboratories, requested withdrawal of approval.

EFFECTIVE DATE: October 27, 1980.

FOR FURTHER INFORMATION CONTACT: Leonard D. Krinsky, Bureau of Veterinary Medicine (HFV–216), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4098.

SUPPLEMENTARY INFORMATION: Jensen-Salsbery Laboratories, Division of Burroughs-Wellcome Co., Kansas City, MO 64108, is sponsor of NADA 7–228 which provides for use of anthelin tablets as a taeniafuge (anthelmintic) in dogs. Each tablet contains 47 milligrams of anthelin (equivalent to 12.7 mg of antimony). The NADA was originally approved January 23, 1950. In their letter of April 29, 1980, the firm requested that approval of the NADA be withdrawn because the product is no longer being manufactured or marketed.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(e), 82 Stat. 345–347 (21 U.S.C. 360b(e))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.84), and in accordance with § 514.115 *Withdrawal of approval of applications* (21 CFR 514.115), notice is given that NADA 7–228 and all supplements for anthelin tablets is hereby withdrawn, effective October 27, 1980.

In a document published elsewhere in this issue of the Federal Register, § 520.120 *(Anthelin tablets* is being revoked.

Dated: October 6, 1980.

Gerald B. Guest,

Acting Director, Bureau of Veterinary Medicine.

[FR Doc. 80-32117 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 80F–0359]

Mitsui Petrochemical Industries, Ltd.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: Mitsui Petrochemical Industries, Ltd., has filed a petition proposing that the food additive regulations be amended to provide for an increase in the weight-percent of units derived from 4-methylpentene-1 in ethylene/4-methylpentene-1 copolymers intended for food-contact applications.

FOR FURTHER INFORMATION CONTACT: Neal D. Singletary, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348)), notice is given that a petition (FAP No. 0B3521) has been filed by Mitsui Petrochemical Industries, Ltd., c/o Keller and Heckman, 1150 17th St. NW., Washington, DC 20036, proposing that § 177.1520 *Olefin polymers* (21 CFR 177.1520) be amended to provide for an increase in the weight-percent units derived from 4-methylpentene-1 in ethylene/4-methylpentene-1 copolymers intended for food-contact applications.

The potential environmental impact of this action is being reviewed. If the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that document will be published with the regulation in the Federal Register in accordance with 21 CFR 25.40(c) (proposed December 11, 1979; 44 FR 71742).

Dated: October 7, 1980.

Sanford A. Miller,

Director, Bureau of Foods.

[FR Doc. 80-32292 Filed 10-16-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 80F–0368]

Radiation Technology, Inc.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: Radiation Technology, Inc., has filed a petition proposing that the food additive regulations be amended to provide for the safe use of a source of gamma radiation to reduce or control microbial contamination in spices, natural flavorings, and dehydrated vegetable seasonings.

FOR FURTHER INFORMATION CONTACT: George H. Pauli, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348)), notice is given that a petition (FAP OM3516) has been filed by Radiation Technology, Inc., Lake Denmark Road, Rockaway, NJ 07866, proposing that Part 179—Irradiation in the Production, Processing and Handling of Food (21 CFR Part 179) be amended to provide for the safe use of a Cobalt 60 or Cesium 137 source of gamma radiation to reduce or control microbial contamination in spices, natural flavorings, and dehydrated vegetable seasonings by irradiating those foods at doses up to 1 megarad. This petition is being evaluated.

The agency has considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and an environmental impact statement is not required. the agency's findings of no significant impact and the evidence

from a crossbow. Most shots of the crossbow impact at an oblique angle to the surface of the skin, so that the dart head never penetrates to the steps but only removes a small piece of flesh and blubber;

d. Removal of such a tissue sample will not cause serious or permanent injury to the whale involved;

e. The skin samples will be subjected to cytological analysis, which will permit, upon examination of stained chromatin material, efficient identification of the sex of each whale;

f. Identification of the sex of the whale at sea would prove useful in establishing the context in which vocalizations are produced, assessing population levels and determining which sex groups, or combinations thereof, comprise the population;

g. This technique of sexing whales, without serious injury, provides a reasonable alternative to more obvious techniques which involve killing animals or attempting to view urogenital openings underwater.

5. Dr. Howard E. Winn, University of Rhode Island, Kingston, Rhode Island 02881, to take one male and one female grey seal pup (*Halichoerus grypus*) for scientific research on the vocal behavior of grey seals.

The Applicant states:

a. The seal pups will be taken from the Basque Islands, Nova Scotia, Canada, between January 15, and February 15, 1974;

b. The seals will be captured using a fish net of heavy cord and transported by truck to the Applicant's facility;

c. The seals will be maintained for three years. At completion of research, the seals will be transferred to an approved facility. Any skeleton or dead specimen will be donated to the Smithsonian Institution;

d. The animals will be maintained in a wooden tank, 20 feet in diameter and six feet deep. The facilities and arrangements for maintaining the seals have been reviewed and found adequate by a licensed veterinarian;

e. The seals will undergo experiments during the first three years of life to determine ontogeny of vocalization, response to playback vocalizations, geographic dialectics, echolocation, activity patterns, auditory discrimination, and a hearing curve. This project is a continuation of the project which commenced in January 1973.

6. Dr. H. L. Stone, Marine Biomedical Institute, University of Texas Medical Branch, 200 University Boulevard, Galveston, Texas 77550, to take 20 marine mammals consisting of California sea lions (*Zalophus californianus*) and/or harbor seals (*Phoca vitulina*) for scientific research on the reflex adjustment of the circulation in the diving reflex.

The Applicant states:

a. The animals will be taken, over a two-year period, from either San Miguel Island or Santa Cruz Island, between November 1 and March 1, using hoop nets;

b. The animals will be taken by professional capturers and transported via air-freight to the Applicant's facility;

c. The animals will be housed in individual pens, six feet wide and eight feet long, with a six foot-by-15 foot-by six foot deep pool. Up to six animals will be on hand at any one time;

d. Dr. Stone has conducted a number of studies on cardiovascular and cerebral physiology and morphology. Other staff members have had practical experience in the handling and maintenance of marine mammals;

e. The current research project is a continuation of a five-year program, which commenced with the receipt of the two animals taken to date, out of ten authorized, which were permitted under a Letter of Exemption granted to alleviate economic hardship;

f. The research project will attempt to determine changes in cerebral and coronary blood flows during a dive and to delineate the neural pathways involved in cardiovascular control;

g. The 20 animals requested are scheduled to be utilized over a period of 24 months. If fewer animals are permitted, the length of time of utilization will be proportionately shortened;

h. The long range goal of this project is an understanding of central nervous system control of heart activities. This understanding may be utilized to facilitate control of heart rate and cerebrovascular disease, through an attempt to reinforce natural reflexes, rather than resorting to chemotherapeutic control systems;

i. The animals will be sacrificed to describe the neuroanatomy, extracranial and intracranial vascular supply, innervation of the circle of Willis, distribution of isotopes within the heart, gross anatomy of the brain, morphology of neuromuscular junction and neural pathways and adaptation.

Documents submitted in connection with these applications are available for viewing at the following locations:

Office of the Director, National Marine Fisheries Service, Washington, D.C. 20235, telephone 202-343-4543 (All applications);

Regional Director, National Marine Fisheries Service, Northeast Region, Federal Building, 14 Elm Street, Gloucester, Massachusetts 01930, telephone 617-281-0640 (Applications No. 4, 5);

Regional Director, National Marine Fisheries Service, Southeast Region, Duval Building, 9450 Gandy Boulevard, St. Petersburg, Florida 33702, telephone 813-893-1841 (Applications No. 4, 6);

Regional Director, National Marine Fisheries Service, Southwest Region, 300 South Ferry Street, Terminal Island, California 90731, telephone 213-548-2575 (Applications No. 1, 3, 6);

Regional Director, National Marine Fisheries Service, Alaska Region, P.O. Box 1668, Juneau, Alaska 99801, telephone 907-586-7221 (Application No. 1);

Regional Director, National Marine Fisheries Service, Northwest Region, Lake Union Building, 1700 Westlake Avenue North, Seattle, Washington 98109, telephone 206-442-7575 (Applications No. 1, 3).

Concurrent with the publication of this notice in the FEDERAL REGISTER the Secretary of Commerce is sending copies of the applications to the Marine Mammal Commission and the Committee of Scientific Advisors.

Pursuant to § 216.15 of the regulations, interested parties may submit written data or views on these applications on January 9, 1974.

Comments should be sent to the Director, National Marine Fisheries Service, Department of Commerce, Washington, D.C. 20235.

All statements and opinions contained in this notice in support of these applications are those of the Applicants and do not reflect the views of the National Marine Fisheries Service.

Dated: December 4, 1973.

WILLIAM F. ROYCE,
Acting Director,
National Marine Fisheries Service.

[FR Doc.73-26135 Filed 12-7-73;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 8897]

FOLIC ACID PREPARATIONS, ORAL AND PARENTERAL FOR THERAPEUTIC USE

Drugs for Human Use; Drug Efficacy Study Implementation; Amendment; Correction

FR Doc. 73-15699 appearing on page 20750 in the issue of Thursday, August 2, 1973, is correct as published. In the FEDERAL REGISTER of October 16, 1973 (38 FR 28710) this document was inadvertently miscorrected by inserting the word "pregnancy" in the first line between the words "alcoholism" and "hemolytic" in the last paragraph of the section headed "Dosage and Administration."

The paragraph, correct as first published, reads as follows:

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

Dated: December 4, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73-26210 Filed 12-7-73;8:45 am]

[DESI 9023; Docket No. FDC-D-568; NDA 9-535]

MALLINCKRODT PHARMACEUTICALS

Antihypertensive Combination Drug Containing Cryptenamine Tannates and Reserpine; Withdrawal of Approval of New Drug Application

On January 30, 1973, there was published in the FEDERAL REGISTER (38 FR 2776) a notice of opportunity for hearing (DESI 9023) in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the new drug applications for

Office of Oil and Gas

COMMITTEE ON PETROLEUM STORAGE CAPACITY NATIONAL PETROLEUM COUNCIL

Notice of Meeting

Pursuant to Executive Order 11686, notice is hereby given of the following meeting:

The Committee on Petroleum Storage Capacity of the National Petroleum Council will meet at 10:a.m. on October 18, 1973, in the National Petroleum Council's Conference Room in Washington, D.C. The agenda will include discussion of an outline, the organizational structure and a work schedule to carry out the petroleum storage capacity study requested by the Secretary of the Interior on July 12, 1973.

The purpose of the National Petroleum Council is solely to advise, inform and make recommendations to the Secretary of the Interior on any matter relating to petroleum or the petroleum industry. The meeting is open to the public to the extent that facilities permit.

Dated October 12, 1973.

J. ROY GOODEARLE,
Associate Director.

[FR Doc.73-22074 Filed 10-13-73;11:13 am]

DEPARTMENT OF COMMERCE

Domestic and International Business Administration

COMPUTER PERIPHERALS, COMPONENTS AND RELATED TEST EQUIPMENT TECHNICAL ADVISORY COMMITTEE

Notice of Meeting

The Computer Peripherals, Components, and Related Test Equipment Technical Advisory Committee of the U.S. Department of Commerce will meet October 23, 1973, at 9:00 a.m. in Room 6802 of the Main Commerce Building, 14th and Constitution Avenue, NW., Washington, D.C.

Members advise the Office of Export Control, Bureau of East-West Trade, with respect to questions involving technical matters, worldwide availability and actual utilization of production and technology, and licensing procedures which may affect the level of export controls applicable to computer peripherals, components, and related test equipment, including technical data related thereto, and including those whose export is subject to multilateral (COCOM) Controls.

Agenda items are as follows:

1. Approval of minutes from Technical Advisory Committee meeting of July 25, 1973.
2. Presentation of papers or comments from the public.
3. Report from chairmen of subgroups and associated discussion.
   a. I/O Equipment Subgroup—L. Wieselman.
   b. Memory Equipment Subgroup—P. Harding.
   c. Test Equipment Subgroup—J. Hubbs.
4. Executive session:
   a. Report from chairmen of subgroups and associated discussion.
      (1) I/O Equipment Subgroup—L. Wieselman.
      (2) Memory Equipment Subgroup—P. Harding.
      (3) Test Equipment Subgroup
   b. Discussion on future assignments.
5. Adjournment.

The Computer Peripherals, Components and Related Test Equipment Technical Advisory Committee was established January 3, 1973, and consists of technical experts from a representative cross section of the industry in the United States and officials representing various agencies of the U.S. Government. The industry members are appointed by the Assistant Secretary for Domestic and International Business to serve a two-year term.

The public will be permitted to attend the discussion of agenda items 1-3, and a limited number of seats—approximately 25—will be available to the public for these agenda items. To the extent time permits, members of the public may present oral statements to the committee. Interested persons are also invited to file written statements with the committee.

With respect to agenda item (4), "Executive session," the Assistant Secretary of Commerce for Administration, on August 13, 1973, determined, pursuant to section 10(d) of Pub. L. 92-463, that this agenda item should be exempt from the provision of Sections 10 (a)(1) and (a)(3), relating to open meetings and public participation therein, because the meeting will be concerned with matters listed in (5 U.S.C. 552(b)(1)).

Further information may be obtained from Rauer H. Meyer, Director, Office of Export Control, Room 1886C, U.S. Department of Commerce, Washington, D.C. 20230 (A/C 202-967-4293).

Minutes of those portions of the meeting which are open to the public will be available 30 days from the date of the meeting upon written request addressed to: Central Reference and Records Inspection Facility, U.S. Department of Commerce, Washington, D.C. 20230.

Dated October 11, 1973.

STEVEN LAZARUS,
Deputy Assistant Secretary for East-West Trade, U.S. Department of Commerce.

[FR Doc.73-22052 Filed 10-15-73;8:45 am]

Office of the Secretary

IMPORTERS' TEXTILE ADVISORY COMMITTEE

Notice of Change of Date of Public Meeting

OCTOBER 15, 1973.

On October 11, 1973, there was published in the FEDERAL REGISTER (38 FR 28091) a notice announcing that a meeting of the Importers' Textile Advisory Committee would be held on October 18, 1973, at 2:00 p.m., Room 6802, Department of Commerce, 14th and Constitution Avenue NW., Washington, D.C. 20230. The purpose of this notice is to advise that the date of that meeting has been changed to October 19, 1973. The time and location of the meeting remain the same.

SETH M. BODNER,
Chairman, Committee for the Implementation of Textile Agreements, and Deputy Assistant Secretary for Resources and Trade Assistance.

[FR Doc.73-22193 Filed 10-15-73;10:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

BASF WYANDOTTE CHEMICALS CORP.

Filing of Petition for Food Additives

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786; (21 U.S.C. 348 (b)(5))), notice is given that a petition (FAP 7J2178) has been filed by BASF Wyandotte Corp., 1609 Biddle Avenue, Wyandotte, Mich. 48192, proposing that § 121.1235 *Copolymer condensates of ethylene oxide and propylene oxide* (21 CFR 121.1235) be amended to provide for the safe use of α-hydro-*omega*-hydroxypoly (oxyethylene)/poly (oxypropylene) (51-57 moles)/poly(oxyethylene) block copolymer, having an average molecular weight of 14,000 and a cloud point above 100° C. in 1 percent aqueous solution, as a dough conditioner in yeast-leavened bakery products.

Dated October 3, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-21924 Filed 10-15-73;8:45 am]

[DESI 5807]

FOLIC ACID PREPARATIONS, ORAL AND PARENTERAL FOR THERAPEUTIC USE

Drugs for Human Use; Drug Efficacy Study Implementation; Amendment

Correction

In FR Doc. 73-15699 appearing on page 20750 in the issue of Thursday, August 2, 1973, in the last paragraph of the section headed "Dosage and Administration", the word "pregnancy" should be inserted in the first line between the words "alcoholism" and "hemolytic".

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of Interstate Land Sales Registration

[Docket No. N-73-196]

ALBERMARLE SHORES

Order of Suspension

In the matter of Albermarle Shores, Administrative Proceedings Division File No. Z-215.

Notice is hereby given that: On June 21, 1973, the Department of Housing and Urban Development, Office of Interstate Land Sales Registration, published in the FEDERAL REGISTER a Notice of Proceedings and Opportunity for Hearing,

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 8897]

FOLIC ACID PREPARATIONS, ORAL AND PARENTERAL FOR THERAPEUTIC USE

Drugs for Human Use; Drug Efficacy Study Implementation; Amendment

In the FEDERAL REGISTER of April 9, 1971 (36 FR 6943), the Commissioner of Food and Drugs published conclusions concerning the effectiveness of folic acid for therapeutic use pursuant to reports received from the National Academy of Sciences-National Research Council.

It was concluded that there is no evidence that doses of folic acid greater than 1 mg. daily have greater efficacy than do those of 1 mg., and that the usual therapeutic dose, oral or parenteral, should be 0.25 mg. to 1.0 mg. daily, and the maintenance dose should ordinarily be 0.1 to 0.25 mg. daily. The notice allowed 180 days for manufacturers and distributors to reformulate products of higher strength than 1.0 mg.

That notice also stated, in accord with regulations then in effect (21 CFR 3.42), that oral preparations supplying more than 0.1 mg. folic acid per dosage unit would be restricted to prescription dispensing and that a dietary supplement furnishing 0.1 mg. could be prescribed when a maintenance level of 0.1 mg. per day was indicated.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner of Food and Drugs has published orders revising regulations for foods for special dietary use and promulgating a standard of identity for dietary supplements and an order revoking § 3.42 and amending the food additive regulations as they apply to folic acid. The effect of these orders is to increase the amount of folic acid which may be added to a food or used in a dietary supplement above the level previously allowed. The maximum daily amount of folic acid now permitted for such use is 0.1 mg. for infants, 0.3 mg. for children under 4 years of age, 0.4 mg. for adults and children 4 or more years of age, and 0.8 mg. for pregnant or lactating women.

Pending review of the status of folic acid by the OTC vitamin-mineral drug panel pursuant to procedures established in § 130.301, the Food and Drug Administration will continue on an interim basis its previous policy of regarding any preparation containing folic acid in excess of the permitted food additive level as a prescription drug.

Therefore, the Commissioner finds it appropriate to amend certain parts of the previous DESI notice for folic acid and republish it as follows:

The Food and Drug Administration has evaluated reports of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, as well as other available evidence, and concludes that folic acid administered orally or parenterally:

1. Is effective for the treatment of megaloblastic anemias of tropical and nontropical sprue, nutritional origin, pregnancy, infancy, and childhood.

2. Lacks substantial evidence of effectiveness in "macrocytic anemias associated with pellagra and similar deficiency states" and such vague, unspecific conditions as "macrocytic anemia of gastrointestinal origin" and "megaloblastic anemias other than pernicious anemia."

The Food and Drug Administration also concludes that there is no evidence that doses of folic acid greater than 1 mg. daily have greater efficacy than do those of 1 mg. The maintenance level of folic acid permitted in food and dietary supplements is up to 0.1 mg. for infants, 0.3 mg. for children under four years of age, 0.4 mg. for adults and children four or more years of age, and 0.8 mg. for pregnant or lactating women. The usual therapeutic dose, oral or parenteral, is up to 1.0 mg. daily.

Dietary supplement preparations are available without a prescription (21 CFR 121.1134). Levels higher than dietary supplement amounts are available only with a prescription.

Parenteral drug products and those oral dosage form products which by reason of containing in excess of 0.8 mg. per dosage unit or per recommended daily dosage or because of a recommended use are limited to prescription dispensing, are regarded as new drugs (21 U.S.C. 321(p)). The Food and Drug Administration is prepared to approve abbreviated new-drug applications and abbreviated supplements to previously approved applications providing for these articles under the conditions described herein.

A. *Form of drug.* Folic acid preparations are in (1) tablet form suitable for oral administration and contain no more than 1.0 mg. folic acid per tablet or (2) solution form suitable for parenteral administration in the dosages recommended in the labeling guidelines below.

B. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations promulgated thereunder, and those parts of its labeling indicated below are substantially as follows: (Optional additional information applicable to the drug, may be proposed under other appropriate paragraph headings and should follow the information set forth below.)

FOLIC ACID

DESCRIPTION

(To be supplied by the manufacturer. This is to be confined to an appropriate description of the physical and chemical properties of the drug, and the formulation.)

ACTIONS

(To be supplied by the manufacturer. This is to be confined to an appropriate statement of the demonstrated pharmacologic/physiologic actions of the active ingredients of the drug in humans. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia in that hematologic remission occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

Oral administration. Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

Parenteral administration. Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

Usual therapeutic dosage—In adults and children (regardless of age) up to 1.0 mg. daily. Resistant cases may require larger doses.

Maintenance level. When clinical symptoms have subsided and the blood picture has become normal, a maintenance level should be used, i.e., 0.1 mg. for infants and up to 0.8 mg. for children under four years of age, 0.4 mg. for adults and children four or more years of age, and 0.8 mg. for pregnant and lactating women, per day, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

Holders of new-drug applications and abbreviated new-drug applications approved for folic acid-containing preparations limited to prescription sale shall submit supplements by October 1, 1973 to provide for revised labeling in accord with that given in paragraph B.2, above.

Any identical, related, or similar product, not the subject of a new drug application, is covered by the new drug applications reviewed and is subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and the Administrative Procedure Act (5 U.S.C. 554) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 26, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15809 Filed 8-1-73;8:45 am]

[DESI 5897; Docket No. FDC-D-365; NDA 5-897, etc.]

FOLIC ACID PREPARATIONS, ORAL AND PARENTERAL FOR THERAPEUTIC USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following folic acid preparations:

1. a. Folvite Elixir; 5 mg. folic acid per 5 cc.;

b. Folvite Tablets; 5 mg. and 20 mg. folic acid per tablet; and

c. Folvite Parenteral Solution; sodium folate equivalent to 15 mg. folic acid per cc.; marketed by Lederle Laboratories, Pearl River, New York 10965 (NDA 5-897).

2. Folic Acid Tablets; 5 mg. per tablet; marketed by Eli Lilly and Co., Box 618, Indianapolis, Indiana 46206 (NDA 6-135).

3. Folic Acid Injection; 15 mg. folic acid, as the sodium salt, per cc.; marketed by S. F. Durst and Co., Inc., 5317 North Third Street, Philadelphia, Pennsylvania 19120 (NDA 6-338).

In addition to the above products, folic acid preparations for therapeutic use are marketed by other firms. A partial list of other suppliers of folic acid preparations limited to prescription dispensing, as indicated in readily available reference sources, is as follows:

ABA Pharmaceutical Co., Division of Bergher Distributing Co.
American Pharmaceutical Co.
American Drug Products.
American Quinine Co.
Approved Pharmaceutical Corp.
Arcum Pharmaceutical Corp.
Associated Labs., Inc.
Barre Drug Co., Inc., The.
Barry-Martin Pharmaceuticals, Inc.
Bell Pharmacal Co.
Carroll Chemical Co., The.
Columbia Medical Co.
Consolidated Midland Corp., CMC Research Division.
Corvit Pharmaceuticals.
Daniels, Robert and Co., Inc.
DuMont Pharmacal Co.
Evron Pharmaceutical Co., Inc.
Faraday Laboratories, Inc.
Gold Leaf Pharmacal Co., Inc.
Gotham Pharmaceutical Co., Inc.
Halsey Drug Co., Inc.
Harvey Labs., Inc.
Jan Labs.
Kirkman Labs., Inc.
Lannett Co., Inc.
Lit Drug Co.
Lustgarten Laboratories, Inc.
Mifflin, McCambridge Co., Inc.
Penhurst Pharmacal Co.
Pharmex, Inc.
Preston Franklin Pharmacal Co.
Richlyn Labs.
Robinson Laboratory, Inc.
Spencer-Mead, Inc.
Stanlabs, Inc.
Supreme Pharmaceutical Co., Inc.
Thompson, Wm. T., Co.
Towne, Paulson and Co., Inc.
Vitamin Research Corp.
Vita-Fore Products Co.
West-Ward, Inc.
Williams Chemical Co.
Winsale Drug Co.

The drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new-drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. Folic acid is effective for the treatment of megaloblastic anemias of tropical and nontropical sprue, nutritional origin, pregnancy, infancy, and childhood.

2. There is a lack of substantial evidence that folic acid is effective for the following labeled indications: "macrocytic anemias associated with pellagra and similar deficiency states" and such vague, unspecific conditions as "macrocytic anemia of gastrointestinal origin" and "megaloblastic anemias other than pernicious anemia."

The Food and Drug Administration also concludes that there is no evidence that doses of folic acid greater than 1 mg. daily have greater efficacy than do those of 1 mg. Further, the usual therapeutic dose, oral or parenteral, should be 0.25 mg. to 1.0 mg. daily, and the maintenance dose should ordinarily be 0.1 to 0.25 mg. daily. Administration of higher doses greatly increases the possibility of masking vitamin B-12 deficiencies and the insidious development of or precipitation of neurological manifestations and/or lesions.

Preparations supplying no more than 0.1 mg. folic acid daily continue to be regarded as dietary supplements (21 CFR 3.42) and may be prescribed when a maintenance dose of 0.1 mg. a day is indicated.

B. *Form of drug.* Folic acid preparations are in (1) tablet form suitable for oral administration and contain no less than 0.15 mg. and no more than 1.0 mg. folic acid per tablet or (2) solution form suitable for parenteral administration in the dosages recommended in the labeling guidelines below.

C. *Labeling conditions.* 1. The label bears the statement "CAUTION: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations promulgated thereunder, and those parts of its labeling indicated below are substantially as follows: (Optional additional information, applicable to the drug, may be proposed under other appropriate paragraph headings and should follow the information set forth below.)

FOLIC ACID

DESCRIPTION

(To be supplied by the manufacturer. This is to be confined to an appropriate description of the physical and chemical properties of the drug, and the formulation.)

ACTIONS

(To be supplied by the manufacturer. This is to be confined to an appropriate statement of the demonstrated pharmacologic/physiologic actions of the active ingredients of the drug in humans. When the mode of action has not been determined, this should be clearly indicated.)

INDICATIONS

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or nontropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid especially in doses above 1.0 mg. daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

Oral administration: Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

Parental administration: Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

Usual therapeutic dosage: In adults: 0.25 mg. to 1.0 mg. daily. *In Children (regardless of age):* 0.25 to 1.0 mg. daily. Resistant cases may require larger doses.

Maintenance dosage: When clinical symptoms have subsided and the blood picture has become normal, a maintenance dose of 0.1 mg. to 0.25 mg. daily should be used, but never less than 0.1 mg. per day. Patients should be kept under close supervision and adjustment of the maintenance dose made if relapse appears imminent.

In the presence of alcoholism, pregnancy, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance dose should be at least doubled.

D. *Previously approved applications.* 1. Each holder of a "deemed approved" new-drug application (i.e., an application which became effective on the basis of safety prior to October 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described herein for the drug, and complete current container labeling, unless recently submitted.

b. Updating information as needed to provide for an oral dosage form containing no less than 01.5 mg. and no more than 1.0 mg. folic acid per tablet or a parenteral dosage form containing an amount appropriate for administration as described herein, and to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new-drug application form FD-356H to the extent described for abbreviated new-drug applications, § 130.4(f), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following time periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling; or, for those products which must be reformulated, 180 days for revised labeling fully in accord with this announcement, provided claims for which substantial evidence of effectiveness is lacking are deleted within 60 days. The supplements should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 180 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement wthin the time periods described in subparagraph 2a.

E. *New applications.* 1. Any person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under A1 above, should submit an abbreviated new-drug application meeting the conditions specified in § 130.4(f) (1) and (2), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein.

2. Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein, except that if the preparation must be reformulated, 180 days will be allowed for the dosage recommendations to be in accord with this announcement.

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new-drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

F. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new-drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A2 of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any such drug for human use offered for the indications for which substantial evidence of effectiveness is lacking, to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing, together with a well-organized and full-factual analysis of the clinical and other investigational data the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety. If a hearing is requested and justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

G. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recomended use is approved in a new-drug application, or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for use other than the use provided for in this announcement, appropriate additional information as described in § 130.4 or § 130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth herein. Requests for such meetings should be made to the Office of Scientific Evaluation at the address given below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

A copy of the NAS–NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 5897, directed to the attention of the following appropriate office, and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD–100), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD–5), Bureau of Drugs.

Request for Hearing (identify with Docket number): Hearing Clerk, Office of General Counsel (GC–1), Room 6–62, Parklawn.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD–5), Bureau of Drugs.

Requests for NAS–NRC report: Press Relations Office (CE–200), 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: March 19, 1971.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.71-4952 Filed 4-8-71;8:46 am]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-202

CORRESPONDENCE

LyphoMed

Orig

December 27, 1985

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 16-70
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/mL - 10 mL vials
Amendment

Dear Dr. Seife:

Reference is made to your letter dated December 19, 1985 for the drug indicated above.

With this amendment, we are providing the test results data for the _____ test on Lot #RD4-218A (EXHIBIT A).

We request that all information in this file be treated as confidential, within the meaning of Regulation 314.11, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your department.

Should you require any additional information, please call the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Director, Regulatory Affairs

DMK/sz

encl.

RECEIVED
DEC 30 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

ANDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illionis 60160

DEC 19 1985

Madam:

Please refer to your abbreviated new drug application submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection, 5 mg/mL, 10 mL Vials.

Reference is also made to your communication dated December 6, 1985.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

The Chicago District laboratory has completed their USP XXI testing of the subject drug product and find the analytical results meet with the USP XXI specifications.

In addition, CHI-DO validated the firm's benzyl alcohol procedure and a _____ test. The benzyl alcohol procedure is suitable for regulatory purposes as modified by CHI-DO laboratory and the results generated for free amine failed to meet the specified limits set forth in the ANDA.

Please comment on _____ test. Submit test results data on Lot #RD-4-218A and any other available lots in duplicate.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Ken Johnson for 12-19-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

JMeyer 12/18/85

CHI-DO
HFN-230
HFN-83
JMeyer/LValenti
R/D INITIALED BY: JMeyer/MSeife
D Utz: 12-18-85 (0140R)
NOT APPROVABLE

LValenti 12/18/85

LyphoMed

Orig

December 6, 1985

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 16-70
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/mL - 10 mL vials
Amendment

Dear Dr. Seife:

Reference is made to your letter dated November 25, 1985 for the drug indicated above.

Reference is also made to the telephone conversation between Mr. Valenti and Mr. Deepak Naik on December 6, 1985 regarding the deficiency letter.

With this amendment we are responding to the comments you have made in your correspondence. For ease of review, our answers are assembled as Items 1 and 2.

We request that all information in this file be treated as confidential, within the meaning of Regulation 314.11, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your department.

Should you require any additional information concerning this submission, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Director, Regulatory Affairs

DMK/sz

encl.

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

NDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illinois 60160

NOV 25 1985

Dear Ms. Komos:

Please refer to your new drug application dated May 22, 1985, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection, 5 mg/mL, 10 mL Vials.

Reference is also made to your communication dated October 7, 1985.

The application is deficient and therefore not approvable under Section 505(b) of the Act for the following reasons:

1. The samples submitted are currently under review by our laboratories.

2. Re-submit stability protocol listing tests that will be performed on the drug product.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our conclusions for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent Johnson /for 11-25-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO
HFN-83
HFN-230
JMeyer/LValenti
R/D INITIALED BY: JMeyer/MSeife 11/22/85
D Utz: 11-18-85 (0018R)
NOT APPROVABLE JMeyer 11/21/85

LyphoMed

Orig

October 7, 1985

RESUBMISSION

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 1670
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/mL - 10 mL vial
Amendment

Dear Dr. Seife:

Reference is made to your letter dated September 26, 1985 for the drug indicated above.

With this amendment we are responding to the comments you have made in your correspondence.

We request that all information in this file be treated as confidential, within the meaning of Regulation 314.11, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your department.

Should you require any additional information concerning this submission, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/mae

Encl.

RECEIVED

OCT 9 1985

GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

LyphoMed

Orig

October 1, 1985

ORIG NEW CORRES

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 1670
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NAI Valentin
10/24/85

Re: ANDA 89-202
Folic Acid Injection, USP
5 mg/mL, 10 mL Vial

Dear Dr. Seife:

Reference is made to your not approvable letter dated September 26, 1985, for the drug indicated above.

As described under 21 CFR 314.120(a), we wish to notify the Division of our **intent to file an amendment** in the near future, answering the deficiencies cited in the application.

Should you have any questions regarding this matter, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Catherine Novilitski /for

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/sz

RECEIVED
OCT 8 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

NDA 89-202

LyphoMed Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illinois 60160

SEP 26 1985

Dear Ms. Komos:

Please refer to your abbreviated new drug application dated May 22, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection, USP, 5 mg/mL, 10 mL Vial.

Reference is also made to your letter dated September 10, 1985 and our letter dated August 20, 1985.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act for the following reasons:

It fails to contain compendial grade inactive materials, clarify.

Please submit Certificate of Analysis from your suppliers certifying that materials are USP/NF grade.

The file is now closed. You are required to take an action described under Section 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our conclusions for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Marvin Seife 9/26/85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO
HFN-83
HFN-230
JMeyer/LValenti Len Valenti 9/25/85
R/D INITIALED BY: JMeyer/MSeife
D Utz: 9-25-85 (0880R)
NOT APPROVABLE
a Kelly 9/25/85

LyphoMed

September 24, 1985

ORIG NEW CORRES

Joseph Brucciani
Food and Drug Administration
3441 South Federal Street
Chicago, IL 60616

Re: NDA 89-202
Folic Acid Injection, USP
(5 mg/mL, 10 mL Vial)

Dear Mr. Brucciani:

Reference is made to the telephone conversation between Mr. Roy Brosdal and Mr. Deepak Naik on September 24, 1985 regarding the additional finished product samples for the above mentioned drug.

As requested we are submitting the following information and the necessary samples to your attention.

1. Ten finished product vials of Folic Acid Injection, USP Lot #RD4-218A.

2. Procedure for the determintion of [redacted] (EXHIBIT - A).

Please contact the undersigned at **(312) 450-7587** if you require any additional information.

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/lm

Encl.

RECEIVED
SEP 26 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

LyphoMed

Orig

September 10, 1985

RESUBMISSION

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 1670
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 89-202
Folic Acid Injection, USP
5 mg/mL - 10 mL
Amendment

Dear Dr. Seife:

Reference is made to your letter dated August 20, 1985 for the drug indicated above.

With this amendment, we are responding to the deficiencies you have indicated in your letter. For ease of review, our response is organized in sequential numbering as appeared on the reviewer's comments.

We request that all information in this file be treated as confidential, within the meaning of Regulation 314.11, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your department.

Should you require any additional information concerning this submission, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/mae

Encl.

RECEIVED

SEP 17 1985

GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

ANDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illinois 60160

SEP 11 1985

Dear Madam:

Please refer to your abbreviated new drug application dated May 22, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection USP, 5 mg/ml, 10 mg/ml Vial.

Reference is also made to your letters dated August 5, 1985 and August 14, 1985. We also reference our letter dated August 20, 1985.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act for the following reasons:

1. The final printed container/carton labels and insert labeling are acceptable.

2. Respond to our letter referenced above.

The file is now closed. You are required to take an action described under Section 314.120 of the Regulations which will either amend or withdraw the application, or if you have substantial disagreement with our conclusions for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Marvin Seife 9/11/85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO

HFN-233
JMeyer/LValenti/MSeife
ft mw 9/9/85 w0631d
Not approved

LValenti 9/9/85
JMeyer 9/9/85

NDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Illinois 60160

AUG 20 1985

Dear Ms. Komos:

Please refer to your abbreviated new drug application dated May 22, 1985; submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Folic Acid Injection, 5 mg/ml, 10 ml vials.

We also acknowledge the receipt of your communication dated July 24, 1985.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act for the following reasons:

1. The samples submitted to our St. Louis and Chicago District Laboratories are currently under review. We will contact you when results become available.

2. It fails to include a description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage and control operations.

3. It fails to describe the educational requirements and experience requirements of personnel to assure the identity, strength, quality and purity of the drug.

4. It fails to include the number of individuals checking weights or volumes of each individual ingredient entering each batch of the drug.

5. It fails to include whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process.

6. It fails to include precautions to check the actual package yield produced from a batch of the drug with the theoretical yield.

7. It fails to include precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling and storage and inventory control.

8. It fails to include additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

9. It fails to include Certificates of Analysis and proprietary specification for inactive ingredients.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our conclusions for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

8/20/85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO
HFN-83
HFN-230
JMeyer/LValenti 8/19/85
R/D INITIALED BY: JMeyer/MSeife
D Utz: 8-19-85 (0729R)
NOT APPROVED
JMeyer 8/19/85

NDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, Il. 60160

AUG 14 1985

Gentlemen:

Reference is made to your request for waiver of in-vivo bioavailability requirements you submitted on May 22, 1985 for Folic Acid Injection USP, 5 mg/ml, 10 ml Vials.

You request has been reviewed by our Division Bioequivalence and they have the following comments:

"The Division of Bioequivalence agrees that the information submitted by LyphoMed, Inc. demonstrates that Folic Acid Injection, USP, 5 mg/ml falls under 21 CFR Section 320.22 (c)(2) of the Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in-vivo bioequivalence requirements be granted for Folic Acid Injection, 5 mg/ml (10 ml vial). From the bioequivalence point of view, the firm has met the in-vivo bioequivalence requirement and the test injectable formulation is deemed to be bioequivalent to Folvite, 5 mg/ml (10 ml) manufactured by Lederle Laboratories."

Sincerely yours,

Marvin Seife 8/14/85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc
BOS-DO
HFN-230
HFN-250
Valenti
MSeife/JSturm/TR/8-13-85
Bio Letter

LyphoMed

August 14, 1985

ORIG NEW CORRES

Mr. Joseph Brucciani
Food and Drug Administration
3441 South Federal Street
Chicago, IL 60616

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/mL - 10 mL vial

Dear Mr. Brucciani:

Reference is made to the telephone conversation between Dr. Lauren Gilbert and Miss. Cathy Norvilitis on August 8, 1985 regarding the analysis of the finished product samples for the above mentioned drug.

As requested we are submitting the following information and the necessary samples.

1. Two finished product vials of Folic Acid Injection, USP Lot #RD4-218A.

2. A vial containing 250 mg of Folic Acid, USP reference standard (Lot #J).

3. A vial containing 500 mg of Leucovorin Calcium reference standard for the system suitability test (Lot #G).

4. Composition of Folic Acid Injection, USP (EXHIBIT - A).

5. Finished Product Specifications for Folic Acid Injection, USP (EXHIBIT - B).

6. Actual Data for Folic Acid Injection, USP Lot #RD4-218A (EXHIBIT - C).

Please contact the undersigned at **(312) 450-7587** if you require any additional information.

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/mae

encl.

RECEIVED
AUG 22 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

LyphoMed

Orig

July 24, 1985

RESUBMISSION

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 1670
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/ml - 10 ml
Amendment

Dear Dr. Seife:

Reference is made to your letter dated July 10, 1985 for the drug indicated above.

With this amendment, we are responding to the deficiencies you have indicated in your letter. For ease of review, our response is organized in sequential numbering as appeared on the reviewer's comments.

We request that all information in this file be treated as confidential, within the meaning of Regulation 314.11, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your department.

Should you require any additional information concerning this submission, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/sz

encl.

RECEIVED
JUL 26 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

NDA 83-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, IL 60160

JUL 10 1985

Dear Mrs. Komos:

Please refer to your abbreviated new drug application dated May 22, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the preparation Folic Acid Injection USP, 5 mg/ml, 10 mL Vial.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act as follows:

1. It fails to include current labeling information. In this regard:

Container: Not Satisfactory

A. Edetate disodium . . . (rather than ~~———~~

B. Following: Protect from Light, add, Retain vial in carton until contents are used (see USP XXI Suppl. 2)

Insert: Not Satisfactory

A. Description
1. L-Glutamic acid, N-[4-[[(2-amino-1, 4-dihydro-4-oxo-6-pteridinyl) methyl]amino]benzoyl]- is the chemical name recognized in the USP.
2. Edetate disodium is the established name.

B. HOW SUPPLIED
1. . . . controlled room temperature.

We request that you revise labels and labeling, then prepare and submit final printed labeling.

2. It fails to contain compendial grade Edetate disodium in the composition of the drug.

3. It fails to include a Drug Master File referral from ———

4. It fails to contain a test for " ——— for the active ingredient and stability protocol. The method is found in the

5. It fails to describe the facilities used in the manufacturing of the product.

6. It fails to include adequate information on filling procedures. Please note the revision "Protect from Light" in the second supplement USP XXI.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

for 7-10-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

CHI-DO

HFN-83
HFN-230 7-9-85
KJohnson/JMeyer/LValenti
R/D INITIALED BY: JMeyer/MSeife
D Utz: 7-8-85 (0515R)
NOT APPROVABLE JMeyer 7/8/85

LyphoMed

File

July 5, 1985

Mr. Donald Page
Food and Drug Administration
Division of Drug Analysis
Room #10002
1114 Market Street
St. Louis, MO 63101

Re: NDA 89-202
Folic Acid Injection, USP
5 mg/ml - 10 ml vial

Dear Mr. Page:

Reference is made to the telephone conversation between Mr. Wayne Vallenti and the undersigned on July 2, 1985 regarding the evaluation of the Folic Acid raw material for the drug indicated above.

As requested, we are submitting the following information and the necessary samples to your attention.

1. Folic Acid raw material sample - ———— (RLM #42359)
2. A vial containing 500 mg of Folic Acid USP reference standard (Lot #J)
3. A Certificate of Analysis from the manufacturer, along with the actual data on raw material analysis (Exhibit A)

Should you require any additional information, please call the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Associate Director, Regulatory Affairs

DMK/sz

encl.

cc: Dr. Marvin Seife

RECEIVED
JUL 11 1985
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

NDA 89-202

LyphoMed, Inc.
Attention: Diane M. Komos
2020 Ruby Street
Melrose Park, IL 60160

JUN 7 1985

Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Folic Acid Injection USP, 5 mg/ml, 10 ml Vial

DATE OF APPLICATION: May 22, 1985

DATE OF RECEIPT: May 24, 1985

We will correspond with you further after we have had the opportunity to review the application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: CHI-DO
HFN-230
MEYER
MSEIFE/DROSEN/jt/6-6-85
ACK 0487A

LyphoMed

May 22, 1985

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Room 1670
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ABBREVIATED
NEW DRUG APPLICATION
89-202

505(j)(2)(A) requirements have been met
DLR 6-6-85

Re: Folic Acid Injection, USP
5 mg/ml - 10 ml vial

Dear Dr. Seife:

The following information is being submitted on behalf of LyphoMed, Inc., pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act.

The information pertains to **Folic Acid Injection, USP** and this submittal along with Form 356H constitute a New Drug Application (regulation #314.1) of the new drug regulations.

We are proposing to market the above referenced product in 5 mg/ml - 10 ml vial.

Our product contains the same active ingredient, strength, indications and routes of administration as the approved marketed product (FOLVITE®) manufactured by Lederle Laboratories, Inc.

Also, Folic Acid Injection, USP manufactured by LyphoMed is identical to the drug product listed under the List of Drug Products Suitable for Abbreviated New Drug Applications, evaluated under the DESI project.

We would appreciate your cooperation in giving this New Drug Application your prompt attention. Should you have any questions or require additional information concerning the submission, please call the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Manager, Regulatory Affairs

DMK/sz
encl.

RECEIVED
MAY 24 1985
GENERIC DRUG

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268

LyphoMed

Patent Certification is Acceptable SHR 2-12-86

February 11, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
(HFN-230) Document Room 17B-20
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

ORIG NEW CORRES

Re: NDA 89-202
Folic Acid Injection, USP

Dear Dr. Seife:

Per Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, please find the revised patent certification statement for the above referenced drug.

Should you have any questions regarding this matter, please contact the undersigned at **(312) 450-7587.**

Sincerely,

Diane M. Komos

Diane M. Komos
Director, Regulatory Affairs

DMK/sz

encl.

RECEIVED
FEB 12 1986
GENERIC DRUGS

LyphoMed, Inc.
2020 Ruby Street • Melrose Park, Illinois 60160
(312) 345-6170 • Telex 206268