

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

87-438

Trade Name: Folicet Tablets, 1.0 mg

Generic Name: Folic Acid

Sponsor: Mission Pharmacal Company

Approval Date: July 30, 1981

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APPLICATION NUMBER:

87-438

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APPLICATION NUMBER:

87-438

APPROVAL LETTER

JUL 30 1981

NDA 87-438

Mission Pharmacal Company
Attention: Neill B. Walsdorf
1365 E. Durango
P.O. Box 1676
San Antonio, TX 78296

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Folicet (Folic Acid) Tablets, 1.0 mg.

Reference is also made to your undated submission received on May 19, 1981, and your submissions dated May 27, 1981 and July 22, 1981 enclosing final printed labeling and additional manufacturing information.

We have completed the review of this abbreviated new drug 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 new drug application, requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

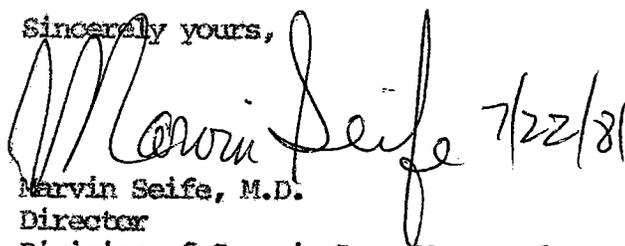
This Administration should be advised of any change in the marketing status of this drug.

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 both copies and a completed form FD-2253, together with a copy of the Final Printed Labeling, to the Division of Drug Advertising (HFD-170). A copy of Form FD-2253 is enclosed for your convenience.

We call your attention to regulation 21 CFR 310.300(b) (3) [or 431.60(b) (3) if Form 6] which requires that material for any subsequent advertising or promotional campaigns, at the time of their initial use, be submitted to our Division of Drug Advertising (HFD-170) with a completed form FD-2253.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

 7/22/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures:

Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD 2253

cc:

DAL-DO

Dup

HFD-614

HFD-313

HFD-530

HFD-5

MSeife/JMeyer/CMSmith

r/d/ init. JMeyer/MSeife 7-21-81

f/t/wh/7-21-81

approved

 7-21-81

**CENTER FOR DRUG
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FINAL PRINTED LABELING

FOLICET™

Folic Acid
TABLETS

DESCRIPTION

Folic Acid, N-[p[(2-Amino-4-hydroxy-6-pteridinyI)-methyl]Amino]benzoyl] glutamic acid, is a complex organic compound present in liver, yeast, and other substances, and which may be prepared synthetically.

Tablets

0.25 mg. Folic Acid

1 mg. Folic Acid

ACTIONS

In man, an exogenous source of folate is required for nucleoprotein synthesis and the 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 is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or non-tropical 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 B₁₂ is deficient.

APPROVED JUL 30 1981

PRECAUTIONS

Folic Acid especially in doses above 0.1 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 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. 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.

HOW SUPPLIED

FOLICETM is supplied in bottles of 100 and 1000 tablets in 0.25 mg. cream colored tablets and 1.0 mg. cream colored tablets.



Rev. 4/81

APPROVED
LOT NUMBER
DATE

NDC 0178 0232 01
FOLICET™
Folic Acid
TABLETS
1.0 mg.
AVERAGE DOSE:
1 tablet daily.
See enclosed circular.
CAUTION: Federal law
prohibits dispensing
without prescription.
100 TABLETS

Warning: Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.



22

APPROVED
LOT NUMBER
DATE

NDC 0178 0232 01
FOLICET™
Folic Acid
TABLETS
1.0 mg.
AVERAGE DOSE:
1 tablet daily.
See enclosed circular.
CAUTION: Federal law
prohibits dispensing
without prescription.
100 TABLETS

Warning: Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.



APPROVED

JUL 30 1981
LOT NUMBER DATE

NDC 0178 0232 01
FOLICET™
Folic Acid
TABLETS
1.0 mg.
AVERAGE DOSE:
1 tablet daily.
See enclosed circular.
CAUTION: Federal law
prohibits dispensing
without prescription.
100 TABLETS

Warning: Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

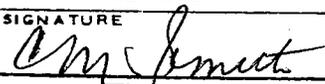


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APPLICATION NUMBER:

87-438

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW <small>(If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)</small>		1. ORGANIZATION HFD-530	2. NDA NUMBER 87-438
3. NAME AND ADDRESS OF APPLICANT (City and State) Mission Pharmacal Co San Antonio, TX 78296		4. AF NUMBER	
6. NAME OF DRUG Folicet		7. NONPROPRIETARY NAME Folic Acid	
8. SUPPLEMENT(S) PROVIDES FOR:		5. SUPPLEMENT(S) NUMBER(S) DATE(S)	
10. PHARMACOLOGICAL CATEGORY vitamin		11. HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC	
13. DOSAGE FORM(S) tablet		14. POTENCY (ies) 1 mg.	
15. CHEMICAL NAME AND STRUCTURE		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
17. COMMENTS Desi # 5897		12. RELATED IND/NDA/DMF(S)	
16. RECORDS AND REPORTS CURRENT <input type="checkbox"/> YES <input type="checkbox"/> NO REVIEWED <input type="checkbox"/> YES <input type="checkbox"/> NO		18. CONCLUSIONS AND RECOMMENDATIONS SEE LETTER REV w/g	
19. REVIEWER NAME C M Smith		SIGNATURE 	
DISTRIBUTION <input type="checkbox"/> ORIGINAL JACKET <input type="checkbox"/> REVIEWER <input type="checkbox"/> DIVISION FILE		DATE COMPLETED 4-15-81	

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW, Page 2		NDA NUMBER
Enter evaluation or comments for each item. If necessary, continue on 8" x 10" paper. Key continuation to item by number. Enter "C" if no change or "NA" if not applicable.		87-438
20. COMPONENTS AND COMPOSITION (6, 7)	Composition	mg per tab
	Folic Acid, USP	1.00
21. FACILITIES AND PERSONNEL (8a,b)	satisfactory	
22. SYNTHESIS (8c)	satisfactory	
23. RAW MATERIAL CONTROLS (8d,e)	inadequate	
a. NEW DRUG SUBSTANCE		
b. OTHER INGREDIENTS	satisfactory	
24. OTHER FIRM(s) (8f)	Drug master file references needed on all manufactures. Satisfactory inspection report needed on _____	
25. MANUFACTURING AND PROCESSING (8g,h,i,k)	satisfactory	
26. CONTAINER (8j)	amber glass with _____	
27. PACKAGING AND LABELING (8l,m)	satisfactory	
28. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (8n)	satisfactory	
29. STABILITY (8p)	no protocol submitted, requested applicant requests 4 year expiration	
30. CONTROL NUMBERS (8q)	to be supplied	
31. SAMPLES AND RESULTS (9)	<p>a. VALIDATION</p> <p>b. MARKET PACKAGE</p>	
32. LABELING (4)	Package insert to be revised...VVKarusaitis	
33. ESTABLISHMENT INSPECTION	applicant in compliance, _____, in compliance	
34. RECALLS		

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF ANDA

DATE COMPLETED: 12/22/80

ANDA #: 87-438

F.R.DATE: 4/9/71
8/2/73
12/10/73

CO. NAME & ADDRESS:
Mission Pharmacal Company
San Antonio, Texas, 78296

NAME OF DRUG: Trade: "FOLICET"
Generic: Folic Acid = 1mg.

DATE OF SUBMISSION: 11/10/80

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1) Review of Studies:

Pertinent data is to be reviewed by the chemist
Bioavailability requirement: NOT required.

2) Review of Labels:

a) Container Labels: Satisfactory
1.0 mg. Tablets Bottles of 100

b) Insert Labeling: UNSatisfactory
Maintenance Dosage: Correct 2nd paragraph, Delete
to wit: in the presence of alcoholism, Hemolytic anemia.....

CONCLUSION: Insert labeling is UNSatisfactory
Container labels are satisfactory
Dr. Standard has made contribution to Dosage and Administration
Section; will add same to insert

RECOMMENDATIONS: The firm is to be so notified.


V.V. Karusaitis, M.D.

cc: Dup
VVK/nms/12/30/80

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87-438

**ADMINISTRATIVE
DOCUMENTS**



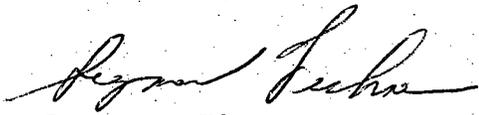
Memorandum

Date . Dec 1, 1980
From Manufacturing Review Branch, HFD-322
Division of Drug Manufacturing
Subject APPROVABLE ANDA 87.438 FOLIC ACID TABLETS
To Director
Division of GENERIC DRUG MONOGRAPHS (HFD 530)
Drug Products
Attn: H.T. BEHRENS **CS**

APPLICANT: MISSION PHARMACEUTICAL CO., SAN ANTONIO, TEXAS P7/80

We have evaluated the operations of _____ as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) with the exception of expiration dating (211.137) and stability testing (211.166) for the referenced application(s). Since you evaluate the applicants' submission of stability data and proposed expiration date, you should make the determination that the stability testing is adequate to support the proposed expiration date. If you desire, you can include appropriate references to (211.137) and (211.166) as deviations directly into your non-approvable letter if you conclude the stability testing is inadequate. Otherwise, we conclude there is no reason to withhold approval of the subject application(s) insofar as CGMP compliance of this/these firm(s) is concerned for the type of operations as specified in this/these pending application(s).

Our evaluation is based in part on Establishment Inspection and Quality Assurance Profile information.


Seymour Fishman

<p align="center">RECORD OF TELEPHONE CONVERSATION/MEETING</p>	<p>DATE July 22, 1981</p>	
<p>After consulting with Mr. Meyer in regards to ANDA 87-438..Folicet (Folic Acid) Tablets by Mission Pharmacal with — tablet in the "How Supplied section of the package insert which was in error, We called Mr. George Alexandrides of Mission who gave us the comittment that he would immediat- edly send twelve copies of the revised insert with the correct color (cream) for the tablet.</p> <p align="center">APPEARS THIS WAY ON ORIGINAL</p>	<p>NDA NUMBER 87-438</p>	
	<p>IND NUMBER</p>	
	<p align="center">TELECON/MEETING</p>	
	<p>INITIATED BY <input type="checkbox"/> APPLICANT/ SPONSOR <input type="checkbox"/> FDA</p>	<p>MADE <input type="checkbox"/> BY TELE- PHONE <input type="checkbox"/> IN PERSON</p>
	<p>PRODUCT NAME Folicet (Folic Acid) Tablet, 1.0 mg</p>	
<p>FIRM NAME Mission Pharmacal San Antonio, Tex.</p>		
<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Mr. George Alexandrides</p> <p>TELEPHONE NO. 512-533-7118</p>		
<p>SIGNATURE CARLOS M. SMITH</p>	<p>DIVISION HFD_530</p>	

NEW DRUG APPLICATION (DRUGS FOR HUMAN USE)

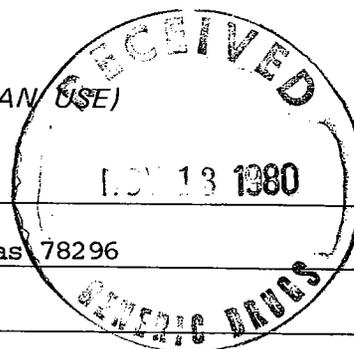
(Title 21, Code of Federal Regulations, § 314.1)

Name of applicant Mission Pharmacal Company

Address 1365 E. Durango, P. O. Box 1676, San Antonio, Texas 78296

Date November 10, 1980

Name of new drug FOLICET



Original application (regulation § 314.1).

Amendment to abbreviated, unapproved application (regulation § 314.6).

Amendment to original, unapproved application (regulation § 314.6)

Supplement to an approved application (regulation § 314.8).

Abbreviated application (regulation § 314.1(f)).

Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §201.100 (21 CFR 201.100). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(e) of the new-drug regulations, and constituting a part of this application are the following:

1. **Table of contents.** The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. **Summary.** A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, and expanded summary and evaluation as outlined in §314.1(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. **Evaluation of safety and effectiveness.** a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. **Copies of the label and all other labeling to be used for the drug** (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §201.100 (21 CFR 201.100). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §310.300 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and control applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper, identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing

history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical method used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §310.3(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §310.3(g) of the new-drug regulations, from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug; *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed

in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Drugs and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and in vitro studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information

concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of HEW, 5600 Fishers Lane, Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example,

outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

h. In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

14. [Reserved]

15. The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

Mission Pharmacal Company

(Applicant)

Per

(Responsible official or agent)

President

(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

Note: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER
87-438
DATE APPROVAL LETTER ISSUED
JUL 30 1981

TO:
Press Relations Staff (HFI-40)

FROM:
 Bureau of Drugs
 Bureau of Veterinary Medicine

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 ABBREVIATED ORIGINAL NDA SUPPLEMENT TO ANDA
CATEGORY: HUMAN VETERINARY

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

DOSAGE FORM: Tablet
HOW DISPENSED: 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, 1.0 mg.

APPEARS THIS WAY
ON ORIGINAL

NAME OF APPLICANT (Include City and State)
Mission Pharmacal Company
San Antonio, TX 78296

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Vitamin

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME
C M Smith

DATE

FORM APPROVED BY

NAME
J L Meyer

DATE

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

87-438

CORRESPONDENCE

Drug
7/29/81

THE SUBMITTED FPL IS SATISFACTORY.

M.S.

NDA 87-438

July 22, 1981

NDA ORIG AMENDMENT

Marvin Seife, M.D.
Director, Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

FPL

Dear Dr. Seife:

This is to amend our previously submitted package insert for FOLICET.

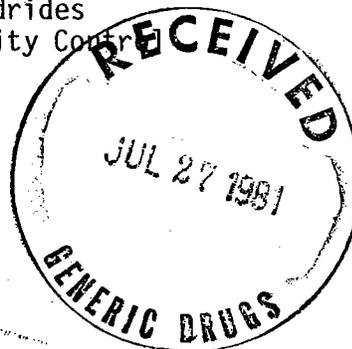
The How Supplied section has been amended in order to replace the tablet color from to cream.

Looking forward to hearing of your final approval, I remain,

Sincerely yours,

George Alexandrides

George Alexandrides
Director Quality Control





Mission
 PHARMACAL COMPANY
 POST OFFICE BOX 1676 SAN ANTONIO TEXAS 78296
 Manufacturer of Fine Pharmaceuticals

9/21/81

Orig

Revise last line of package insert to reflect present color of 1mg tablet. Obtain telephone commitment to do same from firm. If done, may approve applicat
 M.S.
 May 27, 1981

NDA 87-438

Marvin Seife, M.D.
 Director, Division of Generic Drug Monographs
 Office of Drug Monographs
 Bureau of Drugs
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, Maryland 20857

NDA ORIG AMENDMENT

FPL

Dear Dr. Seife:

Pursuant to Mr. Walsdorf's visit with you and your staff on May 19, 1981, we are removing _____ from the formula of FOLICET.

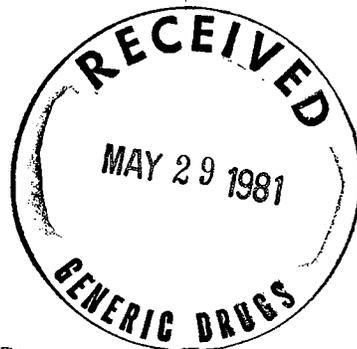
The pages affected by this change have been revised and enclosed herein.

As concerns the Identification and Content Uniformity tests, we have made the appropriate changes to satisfy USP requirements.

Sincerely,

George Alexandrides

George Alexandrides
 Director of Quality Control



APR 16 1981

NDA 87-438

Mission Pharmacal Company
Attention: Neill B. Walsdorf
1365 E. Durango
P. O. Box 1676
San Antonio, TX 78296

Gentlemen:

Reference is made to your abbreviated new drug application dated November 10, 1980 submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Folicet (Folic Acid) Tablets, 1.0 mg.

We have completed the review of this abbreviated new drug application and have the following comments:

- 1) For Labeling:
Revise the package insert, under the Dosage and Administration Section, Maintenance level, 2nd paragraph in accord with the accompanying Federal Register Statement of August 2, 1973.
- 2) For the active ingredient:
 - a) Submit the referenced Drug Master File number for your _____ and a certificate of analysis for _____
 - b) Clarify the listing of _____
- 3) For the excipients:
Include a certificate of analysis for _____
- 4) For the final dosage form:
We note the use of an internal method for the identification test and a modified U.S.P. method for the content uniformity test. Please explain why these were used in lieu of the official U.S.P. methods.
- 5) For Stability:
 - a) We recommend that you consider a two year expiration date based upon the limited stability data. Also include a protocol for, and data derived from, studies of the stability of the drug dosage form, giving physical/chemical observations and testing performed; citing/describing methodology (stability indicating assay) and test conditions and a procedure detecting absence/presence of degradation products.
 - b) A statement that you will perform stability studies on a

minimum of three lots, in accord with your protocol, submit results as they become available and to promptly withdraw from the market any lots that may fall out of specifications.

Please let us have your response as soon as possible.

Sincerely yours,

Marvin Seife 4/16/81

Marvin Seife, M.D.
Director,
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosure: FEDERAL REGISTER statement.

DAL-DO
Dup HFD-530

JLMeyer/CMSmith
rev w/f ft/mms/4/14/81

C.M. Smith 4-15-81
JLMeyer 4/15/81

[DESI 5897; Docket No. FDC-D-265; 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.
 Milfin, 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 342) 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 B₁₂ 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 0.15 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 within 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 recommended 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]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration
[DESI 5897]

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 6843), 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 B₁₂ 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 0.3 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. 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. 73-15699 Filed 8-1-73; 8:45 am]

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 10-12-73; 11:12 am]

DEPARTMENT OF COMMERCE

**Domestic and International Business
 Administration**

**COMPUTER PERIPHERALS, COMPONENTS
 AND RELATED TEST EQUIPMENT TECH-
 NICAL 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 26, 1973.
2. Presentation of papers or comments from the public.
3. Report from chairmen of subgroups and associated discussion.
 - a. I/O Equipment Subgroup—I. Wiesel-
man.
 - 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—I.
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. De-
 partment of Commerce.*

[FR Doc.73-22062 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 As-
 sistant Secretary for Re-
 sources 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- ω -hydroxy-poly (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 5897]

**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,

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 stops but only leaves 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 813-898-1841 (Applications No. 4, 6);

Regional Director, National Marine Fisheries Service, Southwest Region, 300 South Ferry Street, Terminal Island, California 90781, 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 206-442-7675 (Applications No. 1, 2).

Concurrent with the publication of this notice in the FEDERAL REGISTER the Secre-

tary 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 5897]

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