

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
83221

CORRESPONDENCE

~~NDA 83-221~~

AF 10-156

Solar Pharmaceutical Co., Inc.
Attention: Robert Shalman
130 Lincoln Street
Copiahua, NY 11726

JAN 27 1975

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 Probemacid Tablets, 500 mg. with Colchicine 0.5 mg.

Our laboratories have evaluated your samples and have the following comments relating to ANDA specifications and tests:

BEST POSSIBLE COPY

1
Eliar Pharmaceutical Co., Inc.
NDA 83-221

-2-

It is recommended that your specifications and test procedures be appropriately revised and resubmitted.

Please let us have your response promptly.

Sincerely yours, 


Marvin Hais, M.D.

Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

1/27/75

cc:

NYI-80

Dup

HFD-530

HFD-616

HFD-614 *McJusko 1/24/75*

JLMeyer/MAJarski

R/D init. JMeyer/1-20-75

Final typing/rt/1-22-75

rev w/f *JLMeyer 1/24/75*

BEST POSSIBLE COPY

~~NY 10-176~~
NY 10-176

SEP 25 1972

Dejar Pharmaceutical Co., Inc.
Attention: Mr. Robert Madson
130 Lincoln Street
Copenhagen, New York 11706

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 307(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME of DRUG: Probenecid Tablets, 0.5 gr. with Colchicine 0.5 mg.

DATE of APPLICATION: September 18, 1972

DATE of RECEIPT: September 18, 1972

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

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

Sincerely yours,

/S/

low
9/25/72

Harold G. Galt, M.D.
Director
Division of Active Ingredients
New Drug Study Administration
Federal Office
Bureau of Drugs

cc:
NYL-20
Dup
BD-69
BD-66
BD-106
BD-310
JLMeyer/kim/9-21-72
Ack.

JLMeyer 9/21/72

BEST POSSIBLE COPY

~~10-154~~
AF 10-154

Kalar Pharmaceutical Co., Inc.
Attention: Mr. Robert Williams
130 Lincoln Street
Coyne, New York 11726

DEC 29 1972

Gentlemen:

Reference is made to your abbreviated new drug application dated September 12, 1972, submitted pursuant to Section 305(b) of the Federal Food, Drug, and Cosmetic Act for **Probenecid Tablets, 500 mg. with Cefaclorine 0.5 mg.**

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

1. **Container labels:** Submit twelve copies of the printed container labels identical in content to the draft copy.
2. **Package inserts:** Review in accord with the accompanying labeling guidelines.

Other information required by 135.4(f) of the regulations:

1. Clarify the identity of **Excipients** paragraphs in the list of components.
2. Clarify the analytical procedures used to measure the identity, strength, quality, and purity of the components and final dosage form. It is recommended that **pre-approval test methods** (such as you propose for assay of **Excipients** paragraphs) and the testing of the final dosage form be submitted in detail, including test results, and giving complete procedures.
3. Report the **assays** of both active ingredients, **probenecid** and **cefaclorine**.

BEST POSSIBLE COPY

Regarding labeling availability, the requirement for the combination drug products with combination is being deferred at the present time.

Please let us have your response promptly.

Sincerely yours,

cc:
NYL-80
Dup
BD-69
BD-66
BD-105
BD-242

JTBacsanyi/JMeyer/MAJaraki
R/P init. by MClark/JMeyer/12-18-72
Final typing/kim/12-21-72
Enclosure: Labeling Guidelines

M.A. Jaraki
12/26/72

ISI
Marvin S. ...
Director
Division of Action Implementation
Drug Policy Study Implementation
FREDERICK ...
Director of Drug

for
12/29/72

G.T. Baranyi 12-27-72

Rev *v/s*

JMeyer 12/27/72

AF 10-156

FEB 26 1973

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, New York 11726

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 305(b) of the Federal Food, Drug, and Cosmetic Act for Probenecid Tablets, 500 mg. with Colchicine, 0.5 mg.

Reference is also made to your communication dated January 17, 1973, enclosing manufacturing information and a draft package insert.

We have completed the review of this abbreviated new drug application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy.

Other information required by 130.4(f) of the regulations:

A clarification of the analytical procedures routinely used to assure the identity, strength, quality and purity of the final dosage form. In this regard it is to be noted that the combination tablet, probenecid with colchicine, is not a combination form. It is therefore recommended that you submit the specific test methods for assay of the final dosage form.

Please let us have your response promptly.

Respectfully yours,
[Signature] /S/ [Signature] 2/23/73

cc:
NYK-DG

Dup
BD-69 BD-66
BD-106 BD-242

JTBacsanyi/JLMeyer/MJarvis
R/D init. MAClark, JLMeyer 2/15/73
Final typing bhy 2/16/73
Rev. w/f

JTBacsanyi 2/20/73
JLMeyer 2/20/73
JLMeyer 2/20/73

David S. Hill, M.D.
Director
Division of Action Implementation
Drug Safety Study Implementation
Project Office
Bureau of Drugs

BEST POSSIBLE COPY

NDA 83-221

AF 10-156

MAY 15 1973

Dolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, L. I., New York 11726

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 Probenecid Tablets, 500 mg. with Colchicine, 0.5 mg.

Reference is also made to your communications dated February 7, 1973 and March 3, 1973, enclosing manufacturing information and labeling.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

A more complete outline of the methods used in, and the facilities, and controls used for, the manufacture, processing, and packing of the drug since it is noted that the colchicine requires special handling.

To expedite the processing of this application we are requesting copies of the final design form.

Please let us have your response promptly.

Sincerely yours,

MSI
M. Seife, M.D.
Director
Division of Action Implementation
Drug Efficiency Study Implementation
Project Office
Bureau of Drugs

P. D. 5/15/73

cc:
NYK-DO

Dup

BD-69 BD-66

BD-106 BD-242

JTBacsanyi/JLMeyer/MAJarski

R/D init. JLMeyer, MSeife 4/25/73

Final typing bho 5/8/73

Rev. w/f

JLMeyer 5/14/73

BEST POSSIBLE COPY

NDA 83-221

DEC 10 1973

AF 10-156

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

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 Probenacid Tablets, 300 mg. with Calcichino, 0.5 mg.

Reference is also made to your communication dated September 17, 1973, enclosing manufacturing information.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

Clarify the actual/numerical specifications applied to the drug dosage form to assure identity, strength, quality and purity.

In submitting samples and related information previously requested also include: (a) appropriate methodology (for all tests) described in sufficient detail to permit duplication in our laboratories, and (b) your analytical results, as per submitted methodology.

Please let us have your response promptly.

cc:
NYK-DO

Dup
BD-69
BD-66
BD-106
BD-242

JLMeyer/MAJarski
R/D init. by MSeife/JMeyer/12-5-73
Final typing/kim/12-5-73
Rev w/f

W.A. Jarski 12/7/73

JLMeyer 12/7/73

Respectfully yours,
MS
12/10/73
Morton Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

BEST POSSIBLE COPY

NDA 83-221

AF 10-156

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shuman
130 Lincoln Street
Copiague, NY 11726

JUL 25 1974

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 Probenecid Tablets, 500 mg. with Colchicine, 0.5 mg.

Reference is also made to your communication dated April 12, 1974, enclosing samples and related information.

We have completed our review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

Assurance that the specifications and tests applied to the drug dosage form and components are adequate to assure its identity, strength, quality and purity. Relative to this assurance the following comprehensive specifications are recommended for your comment and consideration:

- (a) identification for Probenecid and Colchicine:
 - (1) UV spectra
 - (2) melting points or other suitable determinations
- (b) disintegration: 15 min.
- (c) weight variation
- (d) content uniformity for Colchicine
- (e) assay
- (f) dissolution for Probenecid

BEST POSSIBLE COPY

Please let us have your response promptly.

Sincerely yours,
[Handwritten signature]

IS!
✓ **Marvin Seife, M.D.**
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

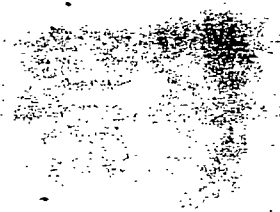
[Handwritten signature]
7/24/74

cc:
NYK-DO
Dup
HFD-107
HFD-8
HFD-106
HFD-13

MAJarski 7/23/74

JLMeyer/MAJarski
R/D init. by MSeife/JMeyer/7-17-74
Final typing/kia/7-19-74
Rev w/f

JLMeyer 7/23/74



Salmon Copy

NDA 83-221

AF 10-156

NOV 07 1974

Bolar Pharmaceutical Co., Inc.
Attention: Mr. Robert Shulman
130 Lincoln Street
Copiague, NY 11726

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 Probenecid Tablets, 500 mg. with Colchicine, 0.5 mg.

Reference is also made to your communication dated September 9, 1974, relating to samples.

We have reviewed the material submitted, and samples and data have been transmitted to our Laboratories for validation. We will correspond with you after their analysis is completed.

The material submitted is being retained in our files.

Sincerely yours,

MS
IS/
Mirvin Seife, R.D.

Director

Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:

NYK-DO

dup

HFD-107 HED-106

HFD-13 HFD-8

JLMeyer/MAJarski

R/D init. JLMeyer, MSeife 11/4/74

Final typing bho 11/4/74

Ack.

MSJarski 11/6/74
JLMeyer 11/6/74

BEST POSSIBLE COPY

RESUBMISSION
NDA ORIG AMENDMENT

BOLAR PHARMACEUTICAL CO., INC.

Orig.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

February 7, 1975

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

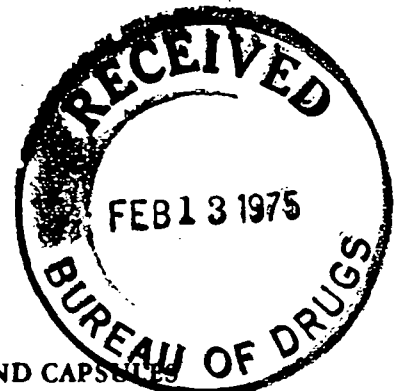
In answer to your letter of January 27, 1975 regarding our abbreviated new drug application for probenecid tablets 500 mg. with colchicine 0.5 mg. enclosed please find comments from our quality control laboratory.

Sincerely,

Robert Shulman
Robert Shulman, President

ENCLS:

Rs/fn



MANUFACTURERS OF PHARMACEUTICAL TABLETS AND CAPSULES

Rev. W/K
RESUBMISSION

NDA ORIG AMENDMENT

E

orig.

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

September 9, 1974

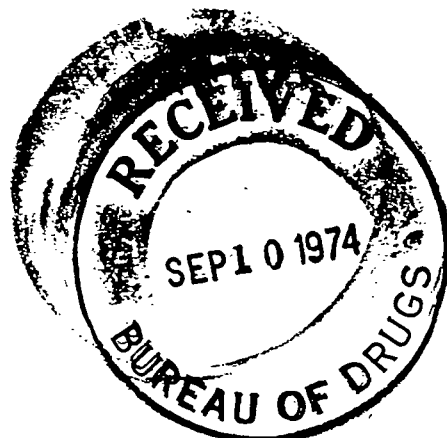
Gentlemen:

In answer to your letter of July 25, 1974 regarding our abbreviated new drug application for Probenecid tablets, 500 mg with Colchicine, 0.5 mg enclosed please find the specifications and tests applied to the drug including dissolution.

Dissolution results on lot # 113505 are also enclosed.

Sincerely yours,


Robert Shulman, President



REV. WIF ✓

RESUBMISSION

BOLAR PHARMACEUTICAL CO., INC. NDA ORIG AMENDMENT

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383

Original

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

April 12, 1974

Gentlemen:

In answer to your letter of December 10, 1973 regarding our abbreviated New Drug Application for Probenecid Tablets, 500 mg. with Colchicine 0.5 mg. enclosed please find the following:

- 1) Three copies of the drug dosage form specifications listing actual numerical specifications are enclosed.
- 2) Three copies of our analytical results on batch number 063192.
- 3) Three copies of appropriate methodology as per your request.

We are enclosing a sample of Probenecid 500 mg. with Colchicine 0.5 mg Tablets, Lot number 063192. On September 17, 1973 we sent two samples of the finished dosage form as per your original request.

Sincerely yours,

Robert Shulman
Robert Shulman, President

DRUG Received in DRUG RM



MANUFACTURERS OF PHARMACEUTICAL TABLETS AND CAPSULES

Rev. W/F Orig E
RESUBMISSION

NDA ORIG AMENDMENT

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-842-8383
NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

September 17, 1973

Gentlemen:

In answer to your letter of May 15, 1973 regarding our abbreviated new drug application for Probenecid 500 mg. with Colchicine 0.5 mg. Tablets.

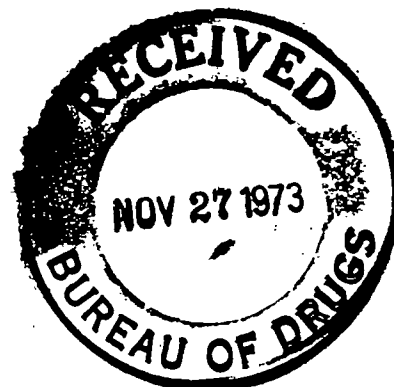
Enclosed please find the following:

- 1) Three copies of "Special Handling for Colchicine."
- 2) Samples of the final dosage form.

Sincerely yours,

Bolar Pharmaceutical Co., Inc.

Robert Shulman
Robert Shulman, President



DRUG Received in DRUG RM

ORIG NEW CORRES

FPL

BOLAR PHARMACEUTICAL CO., INC.

Orig

130 LINCOLN STREET • COPLAGUE, L. I., N. Y. 11726 • 516-MY 1-5454

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

February 7, 1973

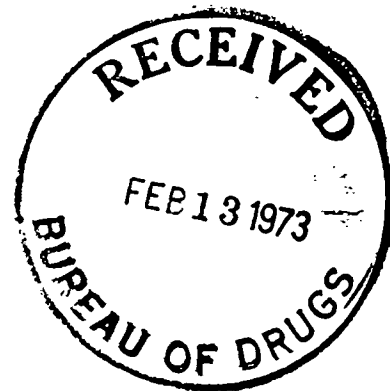
Gentlemen:

As indicated in our letter of January 17, 1973 regarding our abbreviated new drug application for Probenecid Tablets 500 mg. with Colchicine 0.5 mg. enclosed please find twelve copies of the final printed container label.

Sincerely yours,

Bolar Pharmaceutical Co., Inc.

Robert Shulman
ROBERT SHULMAN, PRESIDENT



REV. WJK
RESUBMISSION

FPL

ORIG

NDA ORIG AMENDMENT

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-MY 1-5454

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

March 3, 1973

Gentlemen:

In reference to your letter of February 26, 1973 regarding our abbreviated new drug application for Probenecid Tablets, 500 mg. with Colehicine 0.5 mg. enclosed please find the following:

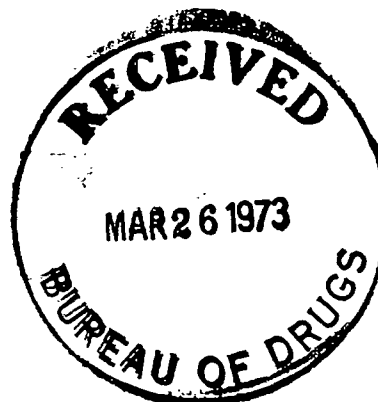
1. Final printed package insert copy.
2. Specific test method for assay of the final dosage form.

The final printed container labels were sent under separate cover on February 7, 1973.

Sincerely yours,

Bolar Pharmaceutical Co., Inc.

Robert Shulman
Robert Shulman, President



Rev. W/F

RESUBMISSION

NDA ORIG AMENDMENT

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • 516-MY 1-5454

NDA 83-221

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

January 17, 1973

Gentlemen:

In reference to your letter of Dec. 29, 1972 regarding our abbreviated new drug application for Probenecid Tablets, 500 mg. with Colchicine 0.5 mg. enclosed please find the following:

1. Draft copy of revised package insert.
2. Suppliers of both active ingredients, probenecid and colchicine.
3. Analytical procedures for Dicalcium Phosphate.

Twelve copies of the printed container labels will be submitted as soon as printing is completed.

Sincerely yours,

BOLAR PHARMACEUTICAL CO., INC.

Robert Shulman
ROBERT SHULMAN, PRESIDENT



the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 11, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-11720 Filed 7-27-72; 8:48 am]

[DESI 12177]

COMBINATION DRUG CONTAINING METHSCOPOLAMINE RESIN AND METHAQUALONE RESIN

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following anticholinergic-sedative drug:

Dimethacol Capsules containing methscopolamine resin and methaqualone resin (formerly called Akalon-T '5' Capsules and Akalon-T '10' Capsules); Strasenburgh Laboratories, Division Pennwalt Corp., 755 Jefferson Road, Rochester, N.Y. 14623 (NDA 12-177).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). The effectiveness classification and marketing status are described below.

A. Effectiveness classification. The Food and Drug Administration has considered the Academy's report, as well as other available evidence, and concludes that this combination drug is possibly effective for its labeled indications.

B. Marketing status. Marketing of such drug with labeling which recommends or suggests its use for indications for which it has been classified as possibly effective may be continued for 6 months as described in paragraphs (d), (e), and (f) of the notice "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273).

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 12177, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

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

Original new-drug applications: Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

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 the authority delegated to the

Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 11, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-11721 Filed 7-27-72; 8:48 am]

[DESI 12383]

COMBINATION PREPARATION CONTAINING PROBENECID AND COLCHICINE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug:

ColBenemid Tablets containing probenecid and colchicine; Merck Sharp & Dohme, West Point, Pa. 19486 (NDA 12-383).

Such 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 drug without approval.

A. Effectiveness classification. The Food and Drug Administration has considered the Academy's report, as well as other available evidence, and concludes that probenecid with colchicine is effective for the treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout.

B. Conditions for approval and marketing. The Food and Drug Administration is prepared to approve abbreviated new-drug applications and abbreviated supplements to previously approved new-drug applications under conditions described herein.

1. **Form of drug.** Probenecid with colchicine preparations are in tablet form suitable for oral administration.

2. **Labeling conditions.** a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the Act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The "Indications" section is as follows:

INDICATIONS

For the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout.

3. **Marketing status.** Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER, July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new-drug applications (i.e., an application which became effective on the basis

of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraphs (a)(1)(i) and (ii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new-drug application, the submission of an abbreviated new-drug application as described in paragraph (a)(3)(i) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 12383, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 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-60), Bureau of Drugs.

Request for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

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 the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 11, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-11723 Filed 7-27-72; 8:48 am]

[DESI 5307]

PARENTERAL MERCURIAL DIURETICS

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 mercurial diuretics for parenteral use:

1. Cumertilin Injectable, containing mercumatilin; Endo Laboratories, Inc., subsidiary of E. I. du Pont de Nemours & Co., Inc., 1000 Stewart Avenue, Garden City, N.Y. 11530 (NDA 7-519).

2. Thiomerin Injection and Thiomerin Lyophilized Powder for Injection, containing sodium mercaptomerin; Wyeth Laboratories, Division American Home Products Corp., Pest Office Box 8299, Philadelphia, Pa. 19101 (NDA 8-355).

3. Mercurhydrin Injection, containing meralluride; Lakeside Laboratories, 1737

Drug, and Cosmetic Act should be labeled in accord with this notice.

The above-named holders of the new-drug applications for these drugs have been mailed a copy of the Academy's report. Any other interested person may obtain a copy of these reports by request to the Food and Drug Administration, Press Relations Office, 200 C Street SW., Washington, D.C. 20204.

Communications forwarded in response to this announcement should be identified with the reference number DESI 12024, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852.

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

Original new-drug applications: Office of Scientific Evaluation (BD-100), Bureau of Drugs.

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

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: February 8, 1971.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 71-3227 Filed 3-8-71; 8:46 am]

[DESI 10126]

POLYOXYETHYLENE DODECANOL, MENTHOL, CAMPHOR, EUCALYPTUS OIL, AND BENZOIN FOR INHALATION

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug:

Vicks Vaposteam Liquid, containing polyoxyethylene dodecanol, menthol, camphor, eucalyptus oil, and benzoin tincture; marketed by Vick Chemical Co., Division of Richardson-Merrell, Inc., 1 Bradford Road, Mount Vernon, N.Y. 10017 (NDA 10-126).

The drug is regarded as a new drug. The effectiveness classification and marketing status are described below.

A. Effectiveness classification. The Food and Drug Administration has considered the Academy's report and concludes that this over-the-counter drug is possibly effective when administered as an inhalant in steam for the relief of cough, stuffiness, and chest congestion.

B. Marketing status. 1. Holders of previously approved new-drug applications and any person marketing any such drug

without approval will be allowed 6 months from the date of publication of this announcement in the FEDERAL REGISTER to obtain and submit in a supplemental or original new-drug application data to provide substantial evidence of effectiveness for those indications for which this drug has been classified as possibly effective. To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well-organized, 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 the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

2. At the end of the 6-month period, any such data will be evaluated to determine whether there is substantial evidence of effectiveness for such uses. After that evaluation, the conclusions concerning the drug will be published in the FEDERAL REGISTER. If no studies have been undertaken or if the studies do not provide substantial evidence of effectiveness, procedures will be initiated to withdraw approval of the new-drug applications for such drugs, pursuant to the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act. Withdrawal of approval of the applications will cause any such drugs on the market to be new drugs for which an approval is not in effect.

The above-named holder of the new-drug application for this drug has been mailed a copy of the NAS-NRC report. Any interested person may obtain a copy of the report by writing to the applicable office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 10126, directed to the attention of the following appropriate office, and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

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

Original new-drug applications: Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Requests for NAS-NRC Reports: Press Relations Office, Food and Drug Administration (CE-200), 200 C Street SW., Washington, D.C. 20204.

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

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: February 8, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 71-3226 Filed 2-8-71; 8:46 am]

[DESI 7898]

PROBENECID

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug:

Benemid Tablets containing probenecid; Merck, Sharp and Dohme, Division of Merck and Co., Inc., West Point, Pa. 19486 (NDN 7-898).

The drug is regarded as a new drug (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 drug 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's report, as well as other available evidence, and concludes that this drug is effective for the indications described in the labeling conditions which follow.

B. Form of drug. This preparation is in tablet form suitable for oral administration.

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. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows:

INDICATIONS

For the treatment of gout and gouty arthritis.

As an adjuvant to therapy with penicillin G, O, or V for elevation and prolongation of penicillin plasma levels by whatever route the antibiotic is given.

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. Adequate data to assure the biologic availability of the drug in the formulation which is marketed. If such data are already included in the application, specific reference thereto may be made.

c. Updating information as needed 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 of 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 periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement 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 biologic availability data.

c. 60 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 within 60 days after the date of this publication, the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement.

E. New applications. 1. Any other 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 A above, should submit an abbreviated new-drug application meeting the conditions specified in § 130.4(f) (1), (2), and (3), published in the FEDERAL REGISTER of April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein and adequate data to assure the biologic availability of the drug in the formulation which is marketed or proposed for marketing.

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.

b. The manufacturer, packer, or distributor of such drugs 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. Exemption from periodic reporting. The periodic reporting requirements of §§ 130.35(e) and 130.13(b) (4) are waived in regard to applications approved for this drug solely for the conditions of use for which the drug is regarded as effective as described herein. The requirements of §§ 130.35(f) and 130.13(b) (1), (2), and (3) remain a continuing responsibility of each applicant.

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 a 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.

A copy of the Academy's report has been furnished to the firm referred to above. Any other interested person may obtain a copy by request to the Food and Drug Administration, Press Relations Office (CE-200), 200 C Street SW., Washington, D.C. 20204.

Communications forwarded in response to this announcement should be identified with the reference number DESI 7898, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 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.

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

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: February 8, 1971.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 71-3224 Filed 3-8-71; 8:46 am]

ATOMIC ENERGY COMMISSION URANIUM ENRICHMENT SERVICES CRITERIA

Charge for Enriching Services

The U.S. Atomic Energy Commission (AEC) hereby announces revisions to the notice entitled "Uranium Enrichment Services Criteria" as published in the FEDERAL REGISTER on December 23, 1966 (31 F.R. 16479), and as amended in 35 F.R. 13546 of August 25, 1970 (referred to herein as the notice).

1. Subparagraphs 5(c) (1), (2), and (3) of the notice are revised to read as follows:

(c) *Charge for enriching services.* (1) The charge for enriching services, in accordance with the Act, will be established on a nondiscriminatory basis and on a basis of recovery of the Government's costs over a reasonable period of time. Applicable charges for enriching services and related services will be those in effect at the time of delivery of enriched uranium to the customer as: (i) published in the FEDERAL REGISTER, or (ii) in the absence of such publication, determined in accordance with the Commission's pricing policy. The charge per unit of separative work for enriching services will be the same as that employed in the Commission's published schedule of charges for sale or lease of enriched uranium. The AEC may impose an appropriate surcharge representing additional costs, if any, to the AEC for providing enriching services on short notice.

(2) AEC's charge for enriching services will be established on a basis that will assure the recovery of appropriate Government costs projected over a reasonable period of time. The cost of separative work includes electric power and all other costs, direct and indirect, of operating the gaseous diffusion plants; appropriate depreciation of said plants; and a factor to cover applicable costs of process development, AEC administration and other Government support functions, and imputed interest on investment in plant and working capital. During the early period of growth of nuclear power, there will be only a small civilian demand on the large AEC diffusion plants. These plants were originally constructed for national security purposes, but will be utilized in meeting future civilian requirements. In this interim period of low plant utilization, the Commission has determined that the costs to be charged to the separative work produced for civilian customers will exclude those portions of the costs attributable to depreciation and interest on plant investment which are properly allocable to plant in standby and to excess capacity.

(3) Projections of supply and demand over a reasonable time period will be used in establishing a plan for diffusion plant operations. This plan will be the basis for establishing an average charge

83 221
ABBREVIATED
NEW DRUG APPLICATION

BOLAR PHARMACEUTICAL CO., INC.

130 LINCOLN STREET • COPIAGUE, L. I., N. Y. 11726 • (516) MY 1-5454

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Attention: DESI Project Office

Gentlemen:

This Abbreviated New Drug Application for a compressed tablet of
PROBENECID 0.5 Gm. with COLCHICINE 0.5 mg.
is submitted to meet the conditions specified in regulation 130.4 (f)
published in the Federal Register of April 24, 1970 and the DESI
announcement on **Probenecid 0.5 Gm with Colchicine 0.5 mg.**
appearing in the Federal Register of July 27, 1972.

Enclosed is a signed form 356H.



Page 1

NEW DRUG APPLICATION (DRUGS FOR HUMAN USE)
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant Bolar Pharmaceutical Co. Inc.

Address 130 Lincoln Street Copliague, N.Y. 11726

Date September 12, 1972

Name of new drug Probenesid 0.5 Gm. with Colechicine 0.5 mg. Tablets

- | | |
|--|---|
| <input type="checkbox"/> Original application (regulation § 130.4). | <input type="checkbox"/> Amendment to abbreviated, unapproved application (regulation § 130.7). |
| <input type="checkbox"/> Amendment to original, unapproved application (regulation § 130.7). | <input type="checkbox"/> Supplement to an approved application (regulation § 130.9). |
| <input checked="" type="checkbox"/> Abbreviated application (regulation § 130.4(f)). | <input type="checkbox"/> 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 § 1.106(b) (21 CFR 1.106(b)). 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 § 130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in § 130.4(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, an expanded summary and evaluation as outlined in § 130.4(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 §1.106(b) (21 CFR 1.106(b)). 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 §130.13 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 the 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 controls 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.

b. 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 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 methods 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 §130.1(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 §130.1(g), 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 the 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 Medicine 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 in 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, 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 Department of HEW, Food and Drug Administration, Bureau of Drugs (BD-200) 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 §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any 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 pre-existing 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.

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 §130.9 of the new-drug regulations concerning supplemental applications.

Bolar Pharmaceutical Co., Inc.

(Applicant)

Per

Robert Schulman
(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.