

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

84279

CORRESPONDENCE

NDA 84-279

AF 42-129

Danbury Pharnacal, Inc.
Attention: Mr. Ira Sacks
131 West Street
Danbury, CT 06810

AUG 29 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 COL-PROBENECID (Probenecid, 500 mg. with Colchicine, 0.5 mg.), Tablets.

We acknowledge receipt of your communication dated February 11, 1975.

We have completed the review of this abbreviated new drug application.

However, before we are able to reach a final conclusion, it will be necessary to have an evaluation of your facility with regard to compliance with current good manufacturing practice by our Division of Drug Manufacturing.

We will correspond with you further when the results of this review become available.

cc:
BOS-DO
dup
HFD-530
HFD-614 HFD-616
JLMeyer/JTaylor
R/D init. JLMeyer, MSeife 8/26/75
Final typing bho 8/26/75
Rev. w/f

Sincerely yours,

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

JLMeyer 8/28/75

8/29/75

NSA 84-279

APR 30 1974

AF 42-129

Sanbury Pharmacy, Incorporated
Attention: Mr. Joe Sachs
131 West Street
Sanbury, Connecticut 06082

Continued:

We acknowledge the receipt of your application for the registration submitted pursuant to section 202(a) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: 2,1-Diphenylpicramide (FEMA # 1000) (0.5 mg.) Tablets

DATE OF APPLICATION: April 16, 1974

DATE OF RECEIPT: April 16, 1974

We will correspond with you during the course of our review of the application to review the application.

We would also like to advise you that we received the original copy of the March 15, 1974 letter to you regarding the registration of the preparation of 2,1-Diphenylpicramide (FEMA # 1000) (0.5 mg.) Tablets. In our report concerning this application, we stated that we were unable to determine that the application was for the registration of the preparation as part of our review. We have now completed our review and we have issued an approval for the registration of the preparation.

Please advise us if you have any questions regarding the application and the FDA's action thereon.

cc: DOS-20

HFD-107 HFD-5

HFD-310

JLH/yr/4/26/74/ylh/yr

R/B init lgr HFD/yr

ACK

RECEIVED
MAY 1 1974
U.S. DEPARTMENT OF HEALTH, EDUCATION & WELFARE
FEDERAL BUREAU OF INVESTIGATION
WASHINGTON, D.C. 20535

Callahan

ISI

4/30/74

York

NDA 84-279

JAN 22 1975

AF 42-129

Danbury Pharmaceutical, Inc.
Attention: Mr. Ira Sachs
131 Main Street
Danbury, CT 06810

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 COL-PROBENECID (Probenecid, 500 mg. with Colchicine, 0.5 mg.) Tablets.

We acknowledge receipt of your communication dated November 12, 1974.

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

1. It is suggested that a suitable assay be performed on the colchicine raw material.
2. It is noted that the full identification test for colchicine in the finished dosage form is not performed. Please clarify.
3. Submit adequate copies of the drug dosage form. Include the methodology for the colchicine content uniformity analysis, and complete results (including spectra) for all tests performed.

Please let us have your response promptly.

Sincerely yours,

ISI

1/22/75

cc:
BOS-DO

dup
HFD-530
HFD-614
HFD-616

JLMeyer/JTaylor
R/D init. JLMeyer
Final typing bbe
Rev. w/f

Handwritten: 1/21/75
Handwritten: 1/20/75
Handwritten: JLMeyer 1/21/75

Harold K. Kato, M.D.
Director
Division of Scientific Policy, Biopharmaceuticals
Office of Drug Research
Bureau of Drugs

JUL 0 2 1974

Danbury Pharmaceutical, Inc.
Attention: Mr. Ira Sachs
131 West Street
Danbury, CT 06810

Gentlemen:

Reference is made to your abbreviated new drug application dated April 18, 1974, submitted pursuant to section 305(b) of the Federal Food, Drug, and Cosmetic Act for **CEL-PROBENECID** (Probenecid 500 mg, with Colchicine 0.3 mg.) Tablets.

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

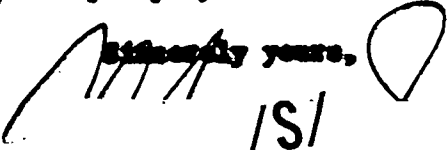
1. The finished dosage form
 - a) Clarify the omission of suitable identification tests for probenecid and colchicine.
 - b) It is suggested that a content uniformity analysis for colchicine be performed.
 - c) It is noted that in the analysis for colchicine that a reference standard is not run concurrently with the sample. Please clarify and specify the source and specifications for the standard used to check the extinction coefficient.
 - d) It is noted that the disintegration test is performed in simulated gastric fluid instead of water as indicated in U.S.P. XVII. Please clarify.
 - e) Clarify the specifications for the weight variation test.
2. Clarify the omission of a microbial limit test for _____
3. It is noted that _____
Submit the specifications and tests applied to the _____
and any special precautions observed in the _____

Danbury Pharamceal, Inc.
NDA 84-279

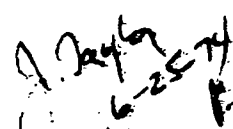
-3-

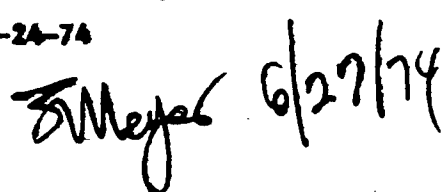
4. It is noted that reference is made to N.F. XII for the specifications and tests applied to Please clarify and submit a supplier's protocol of analysis.
5. It is noted that the test for aldehydes applied to previous does NOT agree with the 3rd Supplement of N.F. XIII. Please clarify.
6. Submit specifications for the containers and closures.
7. It is noted that the directions for the assay of probenecid (p.26) are unclear. Please clarify.

Please let us have your response promptly.

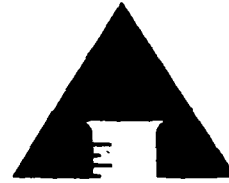
Sincerely yours,  - 11 7/1/74
ISI
Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
BOS-DO
Dup
HFD-106
HFD-107
HFD-13
HFD-8
JBacsanyi/JLMeyer/JMeyer/6-24-74
R/D init. JMeyer/6-24-74
Final typing/rt/6-25-74
rev w/E

 6-25-74
f. Bacsanyi 6-27-74

 6/27/74

Danbury Pharmacal, Inc.



131 West Street · Danbury, Connecticut 06810
Telephone: (203) 744-7200

*Manufacturers
of fine
Pharmaceuticals*

ORIG NEW CORRES

November 4, 1976

FOOD & DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852

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

RE: Col-Probenecid (Probenecid, 500 mg. with Colchicine,
0.5 mg.) Tablets NDA # 84-279

Gentlemen:

Reference is made to our abbreviated new drug application for
Col-Probenecid (Probenecid, 500 mg. with Colchicine, 0.5 mg.)
Tablets NDA # 84-279.

Reference is also made to your communication dated August
29, 1975.

With respect to a satisfactory evaluation, Danbury Pharmacal
has undergone a rigorous inspection which was completed on October
6, 1976, and our facilities were found to be satisfactory. We
were advised that the final report would be sent to you
quickly to help expedite approval of the NDA.

If you require any additional information, please contact us.

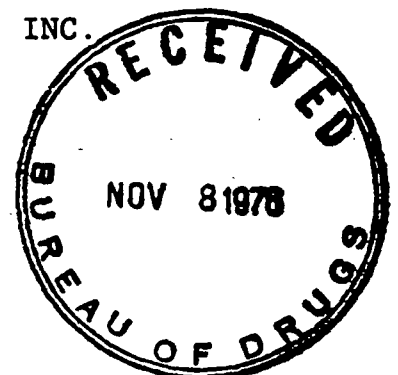
Very truly yours,

DANBURY PHARMACAL, INC.


Ira Sacks
President

| | |
|----------------|------|
| RECEIVED | COPY |
| PHOTOCOPY MADE | |
| FOR DUP | TRIP |

IS/fa



Danbury Pharmacal, Inc.

131 West Street · Danbury, Connecticut 06810
Telephone: (203) 744-7200

November 12, 1974

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

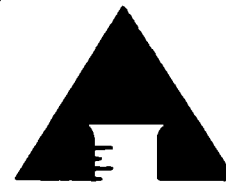
Attn: Marvin Seife, M.D., Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

Gentlemen:

Reference is made to our abbreviated new drug application (NDA 84-279) for Col-Probenecid (Probenecid 500 mg. with Colchicine 0.5 mg.) Tablets. Reference is also made to your communication dated July 2, 1974. Danbury Pharmacal, Inc. hereby submits the following:

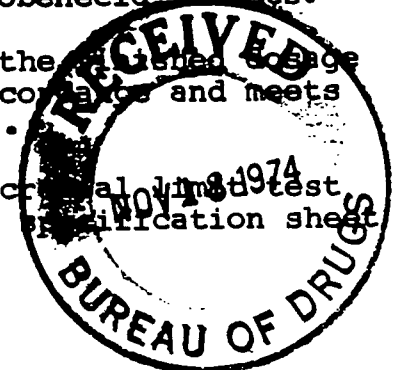
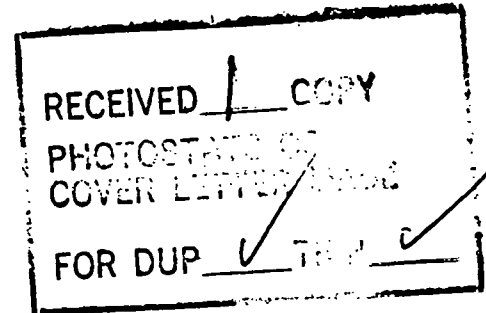
1. a. Danbury Pharmacal, Inc. will perform identification tests for Probenecid and colchicine. Please refer to the revised specification sheet for the finished dosage form Col-Probenecid Tablets and the detailed method of identification.
 - b. Danbury Pharmacal, Inc. is in the process of developing a method for the content uniformity for Colchicine.
 - c. Danbury Pharmacal, Inc. has adopted the method of testing for Colchicine in Col-Probenecid from British Pharmacopia 1973 page 121. Extinction coefficient for colchicine (1 percent, 1 cm.) at the maximum at about 350 mu is 425. (Refer to British Pharmacopia 1973, page 121.) Please refer to the revised method of testing for colchicine in Col-probenecid Tablets.
 - d. The disintegration test for Col-Probenecid shall be performed in water as indicated in the U.S.P. XVIII. Please refer to the revised specification sheet for the Col-Probenecid Tablets.
 - e. The weight variation test performed on the finished dosage form Col-Probenecid Tablets shall be in accordance and meets the requirements of U.S.P. XVIII, page 950.
2. Danbury Pharmacal, Inc. shall perform a microbial test for Please refer to the revised specification sheet

(continued next page)



RESUBMISSION

NDA ORIG AMENDMENT
Manufacturers
of fine
Pharmaceuticals



(Enclosures in original)

November 12, 1974

for also refer to the tests performed on the latest ship-
ment of we received.

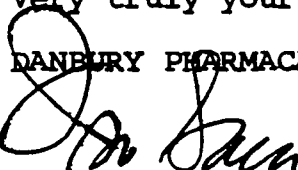
3.

4. Please refer to the revised specification sheet for and suppliers' protocol of analysis.
5. Please refer to the revised specification sheet for Povidone.
6. The containers used shall be new polystyrene amber lightresistant bottles. Please refer to specifications supplied by the manufacturer of the bottles. The closures shall be metal closures with. The manufacturer has a master file with Food and Drug Administration. MF
7. Please refer to the corrected directions for the assay of Probenecid.

Thank you.

Very truly yours,

DANBURY PHARMACAL, INC.



Ira Sacks
President

IS/sm

enc.

Danbury Pharmacal, Inc.



ABBREVIATED
DRUG APPLICATION

131 West Street · Danbury, Connecticut 06810

Telephone: (203) 744-7200

Manufacturers

of fine

Pharmaceuticals

84-279

April 10, 1974

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: DESI 12383; F.R. Vol. 37, No. 146; page (15189);
July 28, 1972

Gentlemen:

Danbury Pharmacal, Inc. hereby submits an abbreviated new drug application for Col-Probenecid Tablets (each tablet contains: Probenecid - 500 mg., Colchicine-0.5mg.), pursuant to Section 505 (b) of the Federal Food, Drug, and Cosmetic Act.

We certify that the methods used in, and the facilities and controls used for the manufacturing, processing, and packaging and holding of the drug are in conformity with current good manufacturing practice in accord with part 133 (21 CFR) of the Regulations.

Thank you.

Very truly yours,

DANBURY PHARMACAL, INC.


Ira Sacks
President



IS/sm

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

Name of applicant Danbury Pharmacal, Inc.

Address 131 West St., Danbury, Connecticut 06810

Date APR 1 1971

Name of new drug Col-Probenecid Tablets

- Original application (regulation § 130.4). Amendment to abbreviated, unapproved application (regulation § 130.7).
- Amendment to original, unapproved application (regulation § 130.7). Supplement to an approved application (regulation § 130.9).
- Abbreviated application (regulation § 130.4(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 § 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.

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 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.

DANBURY PHARMACAL, INC.

(Applicant)

Per

IRA SACKS

(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.

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Danbury Pharmacal, Inc.

131 West Street - Danbury, Connecticut 06810
Telephone: (203) 744-7200



U.S. W.K.E.

RESUBMISSION

NDA ORIG AMENDMENT

Manufacturers
of fine
Pharmaceuticals

Orig

February 11, 1975

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA # 84-279

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

Gentlemen:

Reference is made to our abbreviated new drug application for COL-PROBENECID Tablets (Probenecid, 500 mg. with Colchicine, 0.5 mg.), NDA # 84-279.

Reference is also made to your letter dated January 22, 1975. DANBURY PHARMACAL, INC. hereby submits the following:

1. DANBURY PHARMACAL, INC. will perform an assay on the Colchicine raw material. The assay method is adapted from the British Pharmacopeia, 1973, page 120 - 121.

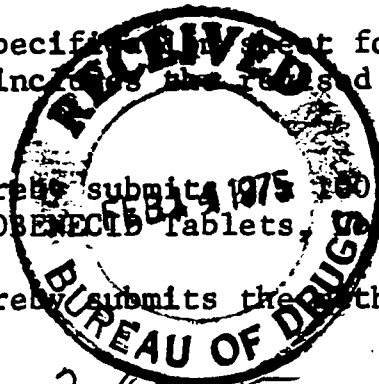
Please refer to the attached Colchicine specification sheet which includes the assay procedure for Colchicine raw material.

2. DANBURY PHARMACAL, INC. will perform the identification test for Colchicine in the finished dosage form as requested.

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Please refer to the attached specification sheet for COL-PROBENECID Tablets, which includes the proposed identification test.

3. a) DANBURY PHARMACAL, INC. hereby submits 100 tablets of the drug dosage form COL-PROBENECID tablets, NDA # 84-279.
- b) DANBURY PHARMACAL, INC. hereby submits the method for



Samples Rec'd w Doc. 2-14-75

DANBURY PHARMACAL, INC.

Re: NDA # 84-279

February 11, 1975

"Content Uniformity Test for Colchicine in COL-PROBENECID Tablets." See attached revised specification sheet for the finished dosage form which includes the "Content Uniformity Test."

c) DANBURY PHARMACAL, INC. hereby submits the complete results of the tests made, including Content Uniformity ~~Test~~ on COL-PROBENECID Tablets, Lot # 9831.

Thank you.

Very truly yours,

DANBURY PHARMACAL, INC.

A handwritten signature in black ink, appearing to read "Ira Sacks", is written over the typed name. The signature is stylized and somewhat cursive.

Ira Sacks
President

IS/ey
Enc.