CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63065

CORRESPONDENCE

Our Reference: 63-065

Danbury Pharmacal, Inc.
Attention: Nessim Maleh
131 West Street
P.O. Box 296
Danbury CT. 06813

Gentlemen:

Please refer to your Abbreviated Antibiotic Drug Application dated August 27, 1988 for Minocycline Hydrochloride Capsules, U.S.P., 100 mg.

We have completed a preliminary review of the submission and conclude that it is unacceptable as an application due to the lack of significant information. Some of the major deficiencies are as follows:

1. Lack of exhibit samples from three batches of drug product.

2. Lack of batch records from three batches of drug product.

3. Lack of room temperature and accelerated stability data three batches of drug product stored in the smallest and largest market container/closure system for three months (assays at 0, 1, 2 and 3 months).

4. Lack of bioequivalence data.

We will begin our review following receipt of all the required information.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch
Division of Generic Drugs

HFD-235
HFD-235/OD
R/D JSinger
R/D init JHarrison
HFD-230/Dr. Seife
9-11-88 bcw 5085d

ANDA 63-065

29 MAR 1989

Danbury Pharmacal, Inc.
Attention: Mr. Nessim Maleh
131 West Street, P.O. Box 296
Danbury, CT 06813

Dear Sir:

Reference is made to the bioavailability study and dissolution data you submitted on October 6, 1988 for Minocycline Hydrochloride Capsules USP, 100 mg.

The study and dissolution data have been reviewed by our Division Bioequivalence and they have the following comments:

"1. The bioequivalence study conducted by Danbury Pharmacal, Inc. on its Minocycline Hydrochloride, 100 mg Capsules, lot # 00755C, comparing it to Minocin^{R}, 100 mg Capsules, lot # 168-494, manufactured by Lederle has been found acceptable by the Division of Bioequivalence. The study demonstrates that Danbury's Minocycline Hydrochloride, 100 mg Capsules are bioequivalent to reference product, Minocin^{R}, 100 mg Capsules manufactured by Lederle Laboratories.

2. The in-vitro test results were also acceptable. The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXI apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than % of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo and in-vitro dissolution testing."

A decision regarding the approvability of an application is not final until the approval letter for that application is issued. Accordingly, any bioequivalence determination communicated in this letter is preliminary. The bioequivalence determination may be revised after a supervisory review of the entire application, upon consideration of the chemistry, manufacturing and controls, labeling, or other scientific or regulatory issues. A revised determination may necessitate an additional study(ies), or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

3/29/89

Irwin Belfe, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-232
DRosen/JHarrison
kl/3-28-89/2236b
bio letters

AADA 63-065

Danbury Pharmacal, Inc.
Attention: Nessim Maleh
131 West Street
P.O. Box 296
Danbury, CT 06813

13 APR 1989

Please refer to your abbreviated antibiotic drug application dated August 27, 1988, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Minocycline Hydrochloride Capsules, USP, 100 mg.

Please also refer to your additional submissions dated August 17, October 6 and December 15, 1988, and January 19 and February 23, 1989.

The application is deficient and therefore not approvable under Section 507 of the Act for the following reasons:

1. The labeling is deficient since the package insert is not the same as Lederle's Minocin insert (3/88). We have enclosed a copy of that insert.

2. The batch records submitted to the application list the following batch sizes:

lot #01218C	capsules
lot #01219C	capsules
lot #00755C	capsules

The batch sizes are too small. Most batch records submitted in applications show a minimum batch size of units. We require that exhibit samples and stability data be generated from batches that are minimally 15% - 20% of the maximum production size and manufactured in production equipment. The application lists a maximum batch size of capsules.

New batches of drug product should be manufactured with a minimum batch size of capsules. New exhibit samples should be submitted, and, new stability data should be generated using the new lots of drug product.

3. the manufacturers of minocycline hydrochloride (bulk), do not have approved Abbreviated Antibiotic Drug Applications for that ingredient.

4. The finished product specifications are unsatisfactory since they do not include the revisions published in the Federal Register on August 26, 1988, pages 32606-32610.

5. The application did not contain in-house release specifications for the finished drug product.

6. The application did not contain an explanation for step of the manufacturing instructions. When will an adjustment be needed?

7. The application did not contain complete room temperature and accelerated stability data from three batches of drug product stored in the smallest and largest container/closure systems for three months (assays at 0,1,2 and 3 months).

   The partial stability data submitted to the application is unsatisfactory since it was generated from batches that are too small.

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

Sincerely yours,

/S/ 4/13/89

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

Enclosure

cc:
HFD-230
HFD-235 /S/ 4/12/89
HFD-235/OD
JMSinger/JHarrison/gp 4/12/89
4/11/89 1515g

AADA 63-065

NOV 9 [illegible]

Danbury Pharmacal, Co.
Attention: Edward M. Cohen, V.P.
131 West St. P.O. Box 296
Danbury, CT 06813

Dear Sir:

Please refer to your abbreviated antibiotic drug application dated August 27, 1988 submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Minocycline Hydrochloride Capsules USP, 100 mg.

We acknowledge receipt of your additional submissions dated April 10 and 18, October 4 and 31, November 27, 1989; January 18, April 25, July 19, and October 29, 1990.

The application is deficient and therefore not approvable under Section 507 of the Act for the following reason:

> The referenced application for the bulk antibiotic has not yet been approved. Until it is, this application will remain not approvable. Once the referenced bulk antibiotic applicant confirms that his/her application has been approved, you may amend your application to advise FDA accordingly.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a minor amendment and should be designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for 11/9/90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

MAR 28 1991

AADA 63-065 (100 mg capsule)
63-181 (50 mg capsule)
63-185 (100 mg tablet)
63-203 (50 mg tablet)

Danbury Pharmacal, Inc.
Attention: Shaheedur Rahman
131 West Street
Danbury, CT 06810

Dear Sir:

Reference is make to your abbreviated antibiotic drug applications for Minocycline Hydrochloride Capsules USP and Minocycline Hydrochloride Tablets USP.

Based upon recent changes in the labeling of MINOCIN (Minocycline Hydrochloride Pellet-Filled Capsules; Lederle, Approved May 31, 1990) we request that you revise your insert labeling. You may use the 1991 PDR as a guide for the labeling revision, except for the following changes:

A. CLINICAL PHARMACOLOGY:

1. Revise the first paragraph to read:

Following oral administration of minocycline hydrochloride capsules or tablets, absorption from the gastrointestinal tract is rapid. Maximum serum concentrations following a single dose of minocycline hydrochloride to normal fasting adult volunteers were attained in 1 to 4 hours. The serum half-life in normal volunteers ranges from approximately 11 hours to 22 hours.

2. Delete the second paragraph and retain the third paragraph.

B. DOSAGE AND ADMINISTRATION:

Revise the second paragraph to read:

Minocycline hydrochloride capsules or tablets may be taken with or without food.

C. DESCRIPTION

Include the structural formula, molecular weight, and molecular formula.

Submit a draft copy of revised insert labeling as an amendment to these unapproved applications.

We await your prompt response.

Sincerely yours,

/S/

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
/S/
HFD-638
jp: 63065.LTR; 03-15-91
KJOHNSON/JPHILLIPS
LETTER OUT

A-003

vs

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

January 19, 1989

Marvin Seife, M.D., Director
Division of Generic Drugs
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
ANDA #63-065

Dear Dr. Seife:

This is in further response to your letter of September 14, 1988.

As promised in our letter of December 15, 1988, Danbury Pharmacal is submitting exhibit samples and batch records for the second and third batches of Minocycline Hydrochlorode Capsules, 100 mg.

The batch production records and analytical results for Control #01218C are shown in Exhibit 1 and those for Control #01219C are shown in Exhibit 2.

Both batches have been entered into our stability testing program. Results will be submitted when they are available.

We are also enclosing one (1) bottle of 200-capsules for each Control Number. For your convenience, one (1) bottle of USP Minocycline Hydrochloride Reference Standard, one (1) bottle of USP Chlortetracycline Hydrochloride Reference Standard and 2 grams of the Minocycline Hydrochloride raw material used to produce batches 01218C and 01219C are included.

Danbury Pharmacal believes that we have met all the preliminary review requirements enumerated in your September 14, 1988 letter. We request that the full review of our submission begin at this time.

Danbury Pharmacal in amending its application to update our raw material specification as per the Federal Register, Volume 53, Number 166, pages 32606-32608, and to add as a raw material supplier. Updated raw material specifications and analytical methodology are shown in Exhibit 3.

Exhibit 4 presents Danbury Pharmacal's analytical results on the raw material, Certificate of Analysis and authorization to refer to recent FDA submission (ANDA on Danbury Pharmacal's behalf.

If you require any additional information, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/joc
enc.

A-002
15

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

December 15, 1988

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
ANDA #63-065

Dear Dr. Seife:

This is in response to your letter dated September 14, 1988.

1. **EXHIBIT SAMPLES**

Only one (1) batch, Control #00755C, was manufactured and samples submitted with our original ANDA submission for this product on August 27, 1988 due to the limited quantity of the bulk active ingredeint at that time.

Additional material will be available momentarily and two (2) additional batches will be manufactured and samples submitted as quickly as possible.

2. **BATCH RECORDS**

As soon as the additional batches will be manufactured, the batch records will be submitted.

3. **STABILITY STUDIES**

The results of the first, second and third months' stability data after storage of Minocycline HCl Capsules, 100 mg, Control #00755C at accelerated conditions of 40°C and 75% relative humidity in the smallest (100's) and largest (1000's) marketed container/closure system are presented in Exhibit 1.

42343

4. BIOEQUIVALENCE DATA

The results of the completed report of the biostudy were submitted to the Agency on October 6, 1988. A copy of the appended letter is given in Exhibit 2.

If you require any additional information, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Milton Blitz
FOR
Nessim Maleh
President

NM/joc
enc.

4-001

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

ok to file
did not completely
respond to our
9/14/88 letter.
J Kruger 10/25/

October 6, 1988

Marvin Seife, M.D., Director
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline
ANDA# 63-065

Dear Dr. Seife:

We are submitting two (2) copies of the completed report of the results of the Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline, Bioavailability/Bioequivalence Study comparing Danbury Pharmacal's formulation of Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline, Control # 00755C with Lederle Laboratories Minocin® Capsules, 100 mg, Control # 168-494, the same lots used in the dissolution study.

The proposed formulation of Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline, Control # 00755C is a production size batch produced with typical production equipment.

We are including another copy of the results of the Dissolution Profile data obtained on the proposed formulation of Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline, Control# 00755C, compared with Lederle's Minocin® Capsules, 100 mg, Control# 168-494. (Exhibit 1)

Exhibits 2 and 3 present the Analytical and content uniformity results for Danbury Pharmacal's Minocycline HCl Capsules, equivalent to 100 mg Minocycline, Control # 00755C.

Sincerely,

DANBURY PHARMACAL, INC.

Milton Blitz
FOR

Nessim Maleh
President

NM/es
enc.

A-005

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

February 23, 1989

Marvin Seife, M.D., Director
Division of Generic Drugs
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD & DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
ANDA# 63-065

Dear Dr. Seife:

Reference is made to our abbreviated new drug application for Minocycline Hydrochloride Capsules, 100 mg NDA# 63-065.

As promised in our letter dated January 19, 1989, enclosed please find stability results after storage for 1 (one) month at 40°C & 75% relative humidity in the smallest and largest container sizes for control numbers 01218C and 01219C. Additional results will be submitted as they become available.

We trust that this meets with your approval.

Sincerely yours,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/fa
enc.

000 831

A-006

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

March 29, 1989

Marvin Seife, M.D., Director
Division of Generic Drugs
Antibiotic Review Branch
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
ANDA #63-065

Dear Dr. Seife:

As requested in your letter dated March 29, 1989 the dissolution test has been incorporated into the manufacturing controls and stability program which is shown in Exhibits 1 and 2 respectively.

The dissolution test will be conducted in 900 mL of water at 37°C using USP XXI apparatus II (paddle) at 50 rpm. The test product will meet the following specifications:

> Not less than % of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

We trust this meets with your approval.

RECEIVED
APR 5 1989

RECEIVED
APR 05 1989
GENERIC DRUGS

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/mm
enc.

000 1651

A-008

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

April 10, 1989

Marvin Seife, M.D., Director
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
ANDA #63-065

Dear Dr. Seife:

Reference is made to our abbreviated new drug application for Minocycline Hydrochloride Capsules, 100 mg, NDA #63-065.

As promised in our letter dated January 19, 1989, enclosed please find stability results after storage for two (2) months at 40°C and % relative Humidity in the smallest and largest container sizes for control #01218C and #01219C. Additional results will be submitted as they become available.

We trust that this meets with your approval.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/joc
enc.

A-001

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

April 18, 1989

Marvin Seife, M.D., Director
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
AADA #63-065

Dear Dr. Seife:

This is in response to the comments contained in your letter dated April 13, 1989.

1. The package insert labeling has been revised according to your recommendations. The revised draft insert is shown in Exhibit 1.

2. Danbury Pharmacal is withdrawing, without prejudice, its batch sizes of capsules. Master formulas for batch sizes of capsules are shown in Exhibit 2. After approval, Danbury Pharmacal will use a batch size of not more than capsules. Process Validation and Stability testing will be performed on the first three (3) batches. When available, the data obtained will be submitted to the Agency, together with a request to begin using the larger batch sizes.

   The three (3) batches submitted, Control Numbers 01218C, 01219C and 00755C, were manufactured in production equipment. The sizes of these batches are a result of the limited supply of Minocycline Hydrochloride raw material currently available.

   As shown in Exhibit 3, the Division of Bioequivalence granted Danbury Pharmacal a waiver from the requirement of a minimum batch size of capsules for Minocycline Hydrochloride Capsules. For your information, our Bioavailability/Bioequivalence Study for this product was approved by the Agency on March 29, 1989. A copy of this approval letter is also shown in Exhibit 3.

3. It is Danbury Pharmacal's understanding that both will be inspected by the FDA shortly. Both firms anticipate speedy approvals for their AADA's after these inspections.

4. Danbury Pharmacal's Minocycline Hydrochloride Capsules, 100 mg, finished product specifications are in compliance with the Federal Register revisions published on August 26, 1988. Exhibit 4 compares the Federal Register specifications with those filed by Danbury Pharmacal.

5. Danbury Pharmacal will use an in-house release specification for the finished drug product of %. This in-house release specification is contained in the revised Analytical Report Sheet shown in Exhibit 5.

6. When capsules are filled in gravity-feed encapsulation equipment, the run weight depends on the density of the blend. If the run weight of the sample capsules from Step of the manufacturing instructions exceeds mg/capsule, the amount of Starch added is the actual run weight achieved, minus mg/capsules, times the number of capsules to be produced. The maximum amount of Starch to be added is %.

   As can be seen from the actual Batch Records submitted, this adjustment was not required for any of the three (3) batches produced.

7. Three (3) months of accelerated and controlled room temperature stability data for batches 01218C and 01219C is shown in Exhibit 6. Three (3) month's of accelerated and controlled room temperature stability data for Batch #00755C was submitted as Exhibit 1 of our December 15, 1988 letter. For your convenience, another copy of the data for this batch is also shown in Exhibit 6.

   In light of the commitments about batch size made by Danbury Pharmacal in item 2 above, we request that this data be accepted by the Agency as demonstrating the stability of our product and the suitability of a twenty-four (24) month expiration date.

We trust that this meets with your approval.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/joc
enc.

A-012

S

Danbury Pharmacal, Inc.

P.O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

January 18, 1990

Acting Director
Antibiotic Review Branch
Attention: Document Control Room
HFD-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules
(Equivalent to 100 mg Minocycline)
AADA #63-065

Gentlemen:

Reference is made to our supplemental application for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline) AADA #63-065 dated November 27, 1989.

As promised, enclosed please find the stability results after storage for one (1) month at challenge conditions of 40°C and % relative humidity in the smallest (50's) and largest (500's) container sizes. Additional stability data will be submitted as it becomes available.

We trust that this meets with your approval.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/joc
enc.

A-011

Danbury Pharmacal, Inc.

P.O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

November 27, 1989

Acting Director
Antibiotic Review Branch
Attention: Document Control Room
HFN-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules
(Equivalent to 100 mg Minocycline)
AADA #63-065

Gentlemen:

Danbury Pharmacal is amending its AADA #63-065, for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline), to provide the results of an additional batch of product which we recently manufactured.

Control #02300C is a capsule batch manufactured with bulk active ingredient. A copy of the Batch Manufacturing Record for Control #02300C is shown in Exhibit 1. Analytical results for Control #02300C are presented in Exhibit 2. Comparative Dissolution Data with the lot of Lederle Minocin® Capsules used in Danbury Pharmacal's approved Biostudy is shown in Exhibit 3.

000 5658

Control #02300C is a capsule production batch. This batch size is due to the limited supply of Minocycline Hydrochloride raw material currently available. As explained in our April 18, 1989, letter to the Agency, we will use a batch size of not more than capsules after approval. Process Validation and Stability Testing will be performed on the first three (3) production batches. When available, the data obtained will be submitted to the Agency, together with a supplement to qualify for larger batch sizes.

If you require any additional information, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/joc
enc.

A-010

J5

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

October 31, 1989

Acting Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Reference: Minocycline Hydrochloride Capsules
Equivalent to 100 mg Minocycline
ANDA 63-065

Gentlemen:

Under the provisions of 21 CFR 314.60, Danbury Pharmacal, Inc. is herewith amending the above-referenced ANDA for Minocycline Hydrochloride Capsules equivalent to 100 mg Minocycline providing for

as consulting laboratory to be used for conducting complete analyses, including stability studies, of the finished drug product and drug components when needed.

Enclosed are the following in support of the above mentioned laboratory:

1. A certificate from
stating that the laboratory is in compliance with the regulations, 21 CFR 210 and 211.

000 5355

2. A letter of authorization from
to refer to this laboratory's Drug Master File (DMF

will use only the methods included in our ANDA to analyze the finished drug product and drug components.

We trust that this meets with your approval.

Sincerely,

DANBURY PHARMACAL, INC.

Shakeel Rahman for

Nessim Maleh
President

NM/mt

Encl.

H.089

JS

Danbury Pharmacal, Inc.

P.O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

FPL for container labels (50, 100 & 500's) are satisfactory 11-13-91

October 4, 1989

Acting Director
Antibiotic Review Branch
Attention: Document Control Room
HFN -235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville,Maryland 20857

Reference: Minocycline Hydrochloride Capsules,
(equivalent to 100 mg Minocycline)
AADA #63-065

Gentlemen:

This is in response to your correspondence dated April 13, 1989. Reference is also made to our correspondence dated April 18, 1989.

We are submitting twelve (12) copies of final printed package insert labeling revised according to your recommendations. This insert labeling has been revised according to the comments in your correspondence dated September 7, 1989 for Minocycline HCL Capsules, 50 mg, AADA #63-181.

Also, enclosed are twelve (12) copies of final printed container labels in 50's, 100's and 500's.

We trust that this meets with your approval.

Sincerely,
DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/IJN
enc.

000 4773

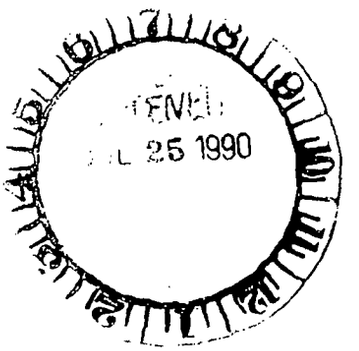
G.C

RCA

Danbury Pharmacal, Inc.

P.O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals



July 19, 1990

Acting Director
Antibiotic Review Branch
Attention: Document Control Room
HFD-635, Room 14-47
FOOD & DRUG Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
AADA # 63-065

Gentlemen:

Danbury Pharmacal would like to update its AADA for Minocycline Hydrochloride Capsules, 100 mg with current information about the status of bulk active ingredient.

received approval for its AADA 63-130 for Minocycline Hydrochloride (Bulk, non-sterile) on May 31, 1990. For your convenience a copy of the approval letter is enclosed.

If you require any additional information, please do not hesistate to contact us.

Sincerely yours,

DANBURY PHARMACAL, INC.

Edward M Cohen

EM Cohen
VP Scientific Operations

EMC/fa
enc.

00010122

ORIGINAL

A-013 ✓

Danbury Pharmacal, Inc.

P. O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

April 25, 1990

Acting Director
Antibiotic Review Branch
Attention: Document Control Room
HFD-235, Room 17-48
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Re: Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline)
AADA #63-065

Gentlemen:

Reference is made to our correspondence to the Agency dated November 27, 1989 in which Danbury Pharmacal amended its AADA for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline) AADA #63-065 to include the results of an additional batch of product (Lot #02300C) manufactured with bulk active ingredient. Reference is also made to our correspondence dated January 18, 1990 in which we submitted one (1) month accelerated stability data for batch #02300C.

As stated in our January 18, 1990 letter, enclosed please find the additional stability results after storage for two (2) and three (3) months at challenge conditions of 40°C and 75% relative humidity in the smallest (50's) and largest (500's) container sizes. This data now completes the cycle of information for three (3) batches of Minocycline Hydrochloride Capsules, 100 mg manufactured with bulk active ingredient. It is our understanding that the material has been found satisfactory by the Antiobiotic Review Branch.

We trust that this meets with your approval.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

RECEIVED
APR 27 1990

NM/joc
enc.

ORIGINAL

11/2/90 Sent To Labeling Reviewer.
JHammel

AL

FPI for insert is Satisfactor
Note: Further revisions will be need post-approv
11-26-90
J. Hall

Danbury Pharmacal, Inc.

P.O. Box 296
131 West Street
Danbury, Connecticut 06810
Telephone: (203) 744-7200
Fax: (203) 798-6161

Manufacturers of fine Pharmaceuticals

October 29, 1990

Division of Generic Drugs
Antibiotic Review Branch
Attention Document Control Room
HFD-235, Room 17-48
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Reference: Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline
AADA 63-065

Gentlemen:

Danbury Pharmacal has revised the final printed package insert labeling for Minocycline Hydrochloride Capsules, equivalent to 100 mg Minocycline, AADA 63-065, in accordance with the comments made during several recent telephone discussions on October 17-26, 1990 between Mr. Richard Adams of the Division of Generic Drugs and several members of our Scientific Operations Staff.

Twelve (12) copies of the revised final printed insert, Revised October 1990, are enclosed.

The October 1990 revision differs from the prior revision of September 1989 in that all specific references to the 50 mg potency product have been deleted:

DESCRIPTION - only ingredients contained in the 100 mg potency capsule are declared.

HOW SUPPLIED - the first paragraph now refers to the 100 mg potency capsule. All references to the 50 mg potency capsule have been deleted.

Revision date - the date of revision is designated as October 1990. Only the product code 5695 is included.

ORIGINAL

A desk copy of this correspondence is being provided to Mr. Adams.

We trust that the package insert labeling changes presented herein meet with the approval of the Agency.

Sincerely,

DANBURY PHARMACAL, INC.

Edward M. Cohen

Edward M. Cohen
Vice President Scientific
Operations

Danbury Pharmacal, Inc.

P. O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

Cant find dup' sent orig to BW 4/10/91

RECEIVED
APR 10 1991
GENERIC DRUGS

April 5,1991

Division of Generic Drugs
Attention: Antibiotic Review Branch Document Control Room
MPN-II, HFD-600
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules, 100 mg
AADA 63-065

Gentlemen:

This is in response to the comments contained in your letter dated November 9, 1990, regarding the approval of the bulk antibiotic submitted in our AADA 63-065 for Minocycline Hydrochloride Capsules, 100 mg.

Danbury Pharmacal Inc. has conducted an additional Bioequivalence study on a batch of Minocycline Hydrochloride Capsules, 100 mg manufactured with bulk active ingredient from
The results of this study are enclosed.

The results of the Biostudy have been reviewed by

A copy of letter to us giving his evaluation of the Biostudy results is shown in Exhibit 1.

Analytical results and comparative dissolution profile for the products used in this study, Danbury's Minocycline Hydrochloride Capsules, 100 mg Control No. 04308C and Lederle's Minocin Pellet-Filled Capsules, 100 mg, Lot No. 268-494, are presented in Exhibit 2.

The Batch Manufacturing Record for Danbury's Minocycline Hydrochloride Capsules, 100 mg Control No. 04308C is shown in Exhibit 3. Examination of this record will demonstrate that the batch used is a production-size batch (theoretical yield

ORIGINAL

capsules, actual yield capsules, see page 8 of the Exhibit) produced with typical production equipment. This batch was produced in exactly the same manner as all batches previously submitted to this AADA.

The Danbury Pharmacal Analytical Report Sheet for the bulk active ingredient used in Danbury's Minocycline Hydrochloride Capsules, 100 mg Control No. 04308C, Control No. C0947P, is shown in Exhibit 4. The manufacturer's Certificate of Analysis for this lot is also included in Exhibit 4.

We have already supplied the agency with stability data on three batches of Minocycline Hydrochloride Capsules 100 mg manufactured with bulk material. These data were sent to the agency on April 29,1990 - lot # 02300C and on April 18,1989 - lot #'s 01218C and 01219C.

If you have any further questions or concerns, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Edward M. Cohen

Edward M.Cohen, Ph.D.
Vice President Scientific Operations

cc: R. Adams (FDA Division of Generic Drugs) no enclosures

EMC/lg

Danbury Pharmacal, Inc.
131 WEST STREET • DANBURY, CT 06810

TELEPHONE (203) 744-7200
TELEFAX (203) 798-6161

July 15, 1991

DRUG NEW CODES

Office of Generic Drugs
Attention: Document Control Room
MPN II, HFD-600
FOOD & DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline)
AADA# 63-065

Gentlemen:

This is in response to a letter dated June 19, 1991 from Dr. Carl Peck, regarding inclusions of only those facilities currently capable of their designated roles in the applications to the FDA.

Danbury Pharmacal is amending AADA 63-065 for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline) to withdraw as alternate testing laboratories. Danbury Pharmacal will utilize to perform testing of quality control, process validation and stability samples, using the methods specified in this ANDA, when necessitated by laboratory workloads. will also serve as an alternate laboratory to our approved in-house Microbiology laboratory, for Microbial Limit Tests and other required Microbiological Assays.

If you have any further questions or concerns, please do not hestiate to contact us.

Noted: NAT. for N-w
This should be reviewed in conjunction with amendment 4/15/91
10/9/91

Sincerely,

DANBURY PHARMACAL, INC.

Edward M. Cohen, Ph.D.
Vice President
Scientific Operations

EMC/fa

Danbury Pharmacal, Inc.
131 WEST STREET • DANBURY, CT 06810

TELEPHONE (203) 744-7200
TELEFAX (203) 798-6161

ORIGINAL

August 7, 1991

Office of Generic Drugs
Attention: Document Control Room
MPN II, HFD-600
FOOD & DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline)
AADA 63-065

Gentlemen:

This correspondence is in response to a number of different telephone discussions with members of your Office of Generic Drugs regarding the packaging of Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline), AADA 63-065.

The container closure system used to package the product for stability testing is confirmed to be comprised of the following components:

BOTTLE: High Density Polyethylene (HDPE) made of ; Pages 322-346 in our AADA 63-065 provided the details of the physical dimensions and other appropriate specifications for the resin and bottle.

The designation of polyethylene bottles on the stability reports is incomplete. Danbury Pharmacal used High Density Polyethylene bottles for the stability packaging of the ANDA batch, and will use HDPE bottles for packaging of commerical goods.

CLOSURE: Metal cap with pressure sensitive liner manufactured by ; pages 369-377 in our AADA provided the details for the physical dimensions and other appropriate specifications for the closure.

STUFFER: will be used as the stuffer under the Container/Closure System. The designation of cotton on the stability reports is an error. Danbury Pharmacal has always used USP as the stuffer. Future stability reports will be corrected.

With respect to packaging of the product for commerical distribution, after approval of the AADA, Danbury Pharmacal advised the agency that the source of the HPDE resin for the bottles will be resin Enclosed with this correspondence are copies of the appropriate DMF references and other testing information on the resin. This information replaces pages 322-346 in the AADA which refer to the use of resin and bottles produced therefrom. It should be noted that the physical characteristics of the HDPE bottles produced from the and those produced from the resin are essentially the same. Stability study sheets will be updated to specifiy the use of the resin bottles. After approval of the AADA for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline). Danbury Pharmacal commits to placing the first three production lots of product on stability tesing in accordance with the firm's Post-Approval Stability Protocol.

We trust that this correspondence addresses all of the issues raised by the agency for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline), AADA 63-065.

Sincerely,

DANBURY PHARMACAL, INC.

Loren Geller for

Edward M. Cohen, Ph.D.
Vice President
Scientific Operations

EMC/fa
enc.

Noted:
To R. Adams
Mark Anderson 10/25/91

Danbury Pharmacal, Inc.
131 WEST STREET • DANBURY, CT 06810
TELEPHONE (203) 744-7200
TELEFAX (203) 798-6161

MINOR AMENDMENT

October 15, 1991

Office of Generic Drugs
Attention: Antibiotic Review Division Document Control Room
MPN II, HFD-636
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

N-000

RECEIVED
NDA ORIG AMENDMENT OCT 21 1991
GENERIC DRUGS

Reference: Minocycline HCl Capsules (equivalent to 100 mg Minocycline)
AADA 63-065

Gentlemen:

This is in response to several telephone discussions with Mr. Richard Adams of your Antibiotic Review Division regarding Minocycline HCl Capsules (equivalent to 100 mg Minocycline) AADA 63-065.

1. As requested, the specifications for _____ and other impurities are both stated as not more than ____ % each. These specifications can be found on the initial Analytical Report Sheets and the Stability Study data report forms. Revised Analytical Report Sheets are shown in Exhibit 1; revised Stability Study reports are shown in Exhibit 2.

The documents in Exhibit 1 supersede page 163 of our original ANDA, Exhibit 1 page 13 and Exhibit 2 page 13 of our January 19, 1989 letter to the Agency, and Exhibit 2 of our November 29, 1989 letter to the Agency. The documents in Exhibit 2 supersede Exhibit 1 of our December 15, 1988 letter to the Agency, the enclosures with our April 10, 1989 letter, Exhibit 6 of our April 18, 1989 letter to the Agency, the enclosures with our January 18, 1990 letter to the Agency, and the enclosures with our April 25, 1990 letter to the Agency.

As a result of our ongoing in-house auditing activities, minor transcription errors in these documents have been corrected.

2. The requested tabulation of the extraction solvent for the minocycline from the dosage form used in any particular assay is noted in Exhibit 3.

3. The requested tabulation of the impurity levels in raw materials and finished product batches is shown in Exhibit 4.

4. Stability data for Minocycline HCl Capsules (equivalent to 100 mg Minocycline) Control No. 04308C is presented in Exhibit 5. This batch was used in the Bioequivalence study which we submitted April 5, 1991.

ORIGINAL

We believe that the stability data submitted for the product fully supports our petition for a 24 month expiration period for the product stored at controlled room temperature.

Finally, the pre-approval inspection of the subject product by the Buffalo District office has been completed.

If you have any further questions or concerns, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Edward M. Cohen

EMC/lg

Edward M. Cohen, Ph. D.
Vice President Scientific Operations

Draft labeling needs revision 6-10-91 J Phillips

Danbury Pharmacal, Inc.

P. O. Box 296
131 West Street
Danbury, Connecticut 06810

Manufacturers
of fine
Pharmaceuticals

May 17, 1991

Office of Generic Drugs
Attention: Document Control Room
MPN II, HFD-600
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Reference: Minocycline Hydrochloride Capsules (equivalent to 100 mg Minocycline)
ANDA 63-065

Gentlemen:

This is in response to the comments contained in your letter dated March 28, 1991 regarding the labeling of Minocycline Hydrochloride Capsules (equivalent to 100 mg Minocycline), AADA 63-065.

The insert has been revised as requested, using the 1991 PDR and the comments in your letter. The requested draft insert is shown in Exhibit 1 and the 1991 PDR copy followed is shown in Exhibit 2.

This insert includes both Minocycline Hydrochloride Capsules and Minocycline Hydrochloride Tablets. If the Agency decides to approve one of these products before the other, Danbury Pharmacal will prepare final printed insert labeling including only those products which will be approved.

Revised packaging standards for Minocycline Hydrochloride Capsules (equivalent to 100 mg Minocycline) are shown in Exhibit 3. These packaging standards, which supercede those on pages 385-387 of our original ANDA, include revisions and corrections to the capsule imprint, cap (50-capsule bottles must have a Saf-Lok cap, while 100-capsule bottles may have either a metal or Saf-Lok cap), intermediate package, shipping carton and note. Specifications for the Saf-Lok cap, which is a plastic overcap on our standard metal cap to render the cap child resistant, are also included in Exhibit 3.

Please note that a second Bioavailability study supporting this AADA was submitted to the Agency on April 5, 1991.

If you have any further questions or concerns, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

E M Cohen

EMC/lg

Edward M. Cohen, Ph. D.
Vice President Scientific Operations

* Not Enough Labeling Sent

Danbury Pharmacal, Inc.
131 WEST STREET • DANBURY, CT 06810

TELEPHONE (203) 744-7200
TELEFAX (203) 798-6161

FPL for insert labeling is satisfactory 11-13-91
TELEPHONE AMENDMENT
J Phillips

November 1, 1991

Office of Generic Drugs
Attention: Antibiotic Review Branch Document Control Room
MPN-II, HFD-600
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

N-000 AL

Reference: Minocycline Hydrochloride Capsules (Equivalent to 100 mg of Minocycline)
AADA 63-065

Gentlemen:

Danbury Pharmacal is submitting the enclosed final package insert labeling for Minocycline Hydrochloride Capsules (equivalent to 100 mg Minocycline) AADA 63-065. This labeling has been revised to include the changes discussed with Mr. Jerry Phillips of your Office.

As discussed on October 30, 1991 with Mr. Phillips, we have changed Minocycline Hydrochloride Capsules to minocycline hydrochloride capsules where specifically requested. In the DOSAGE AND ADMINISTRATION section regarding children above 8 years of age, second paragraph, we have changed Minocycline Hydrochloride Capsules to minocycline.

We trust that we have completed all the requirements for approval of this ANDA.

Sincerely,

DANBURY PHARMACAL, INC.

Loren Gelber for

Edward M. Cohen, Ph.D.
Vice President, Scientific Operations

EMC/eclg

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Vol. 4.1

Danbury Pharmacal, Inc.
131 WEST STREET • DANBURY, CT 06810

TELEPHONE (203) 744-7200
TELEFAX (203) 798-6161

N-000 AC

ORIGINAL AMENDMENT

TELEPHONE AMENDMENT

November 22, 1991

Office of Generic Drugs
Attention: Antibiotic Review Branch Document Control Room
MPN II, HFD-600
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

SPECIAL

Reference: Minocycline HCl Capsules (equivalent to 100 mg Minocycline)
AADA 63-065

Gentlemen:

This is in response to a telephone request received November 20, 1991 from Mr. David Doleski, CSO, of your Office, regarding Minocycline HCl Capsules (equivalent to 100 mg Minocycline) AADA 63-065.

Danbury Pharmacal is withdrawing without prejudice as an alternate testing laboratory, due to the situation which is described in the enclosed letter. When the situation is resolved and the firm satisfies all FDA requirements, we intend to submit a supplement, after approval of this AADA, to reinstitute as an alternate laboratory.

We believe that we have now fully responded to all of the Agency's outstanding concerns regarding this AADA and that it is now ready for immediate approval.

Sincerely,

DANBURY PHARMACAL, INC.

Edward M. Cohen

Edward M. Cohen, Ph. D.
Vice President Scientific Operations

EMC/lg

cc: D. Doleski (fax)

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NOV 25 1991
GENERIC DRUGS

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63-065 (JS)

Danbury Pharmacal, Inc.

131 West Street · P.O. Box 296
Danbury, Connecticut 06813
Telephone: (203) 744-7200

Manufacturers
of fine
Pharmaceuticals

August 27, 1988

Marvin Seife, M.D., Director
Antibiotic Review Branch
Attention: Document Control Room
HFN-535, Room 17-48
FOOD & DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Reference: Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline)
Abbreviated New Drug Application

Gentlemen:

Danbury Pharmacal, Inc., herewith submits an abbreviated new drug application for Minocycline Hydrochloride Capsules (Eq. to 100 mg Minocycline) pursuant to Section 505 (j) 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, packaging and holding of the above mentioned drug are in conformity with the Current Good Manufacturing Practices in accord with Part 210 (21 CFR) of the Regulations.

This ANDA for Minocycline Hydrochloride Capsules (Eq. to 100 mg Minocycline) is identical to Lederle Laboratories Minocin^{R} Capsules, 100 mg (Brand of Minocycline Hydrochloride Capsules) product previously approved by FDA, which is listed in the "Approved Prescription Drug Products" 7th Edition, page (please refer to Label and Labeling Section).

The labeling is the same as the labeling for Lederles Minocin^{R} Capsules, 100 mg (brand of Minocycline Hydrochloride Capsules) manufactured by Lederle as published in the latest PDR, 1988, 42nd Edition (please refer to Label and Labeling Section), except for the HOW SUPPLIED AND DESCRIPTION SECTIONS in which the proposed formulated product is described (please refer to Label and Labeling Section).

30393

Danbury Pharmacal, Inc. commits that the finished product and components comply with the specifications described under tab K, pages 157-214.

Data for one batch is included under Tab K. The second and third batches will be manufactured as soon as additional bulk active ingredient is available and the results will be forwarded to the Agency. Samples of the first lot is enclosed with this submission. Additional samples of the second and third batches will be forwarded to you as they become available.

The Bioavailability/Bioequivalence Study is being conducted on Danbury Pharmacal's Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline) and Lederle's Minocin® Capsules by

The results and full report will be submitted when they become available.

DISSOLUTION INFORMATION:

For your reference, comparative dissolution profile data with Lederle's Minocin® Capsules, 100 mg are presented on pages 3-9.

For your ready reference, we are submittity two (2) additional copies of the analytical methodology for Minocycline Hydrochloride Capsules (Equivalent to 100 mg Minocycline).

Thank you.

Sincerely yours,

DANBURY PHARMACAL, INC.

Nessim Maleh
President

NM/fa
enc.

Ken's

Danbury Pharmacal, Inc.

P.O. Box 990
12 Stoneleigh Avenue
Carmel, New York 10512
Telephone: (914) 225-1700

Manufacturers
of fine
Pharmaceuticals

August 17, 1988

Dr. Charles Ise
Division of Bioequivalence
Attention: Document Control Room
HFN-250, Room 17B-06
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

REQUEST FOR WAIVER

REFERENCE: Minocycline HCl Capsules, 100 mg

Dear Dr. Ise:

This is a request for a waiver from conducting a Biostudy on a unit Batch Size.

A proposed formulation of Minocycline HCl Capsules, 100 mg, potency as typified by Control #00755C, consisting of capsules is a production size batch manufactured with production equipment with a total weight of kg of blend. The reason why we are making a capsule batch is the extremely limited availability of bulk active ingredient at this time.

Based on the above, we request a waiver from conducting the Biostudy on a unit Batch to be able to run the Biostudy on the capsule lot for this product.

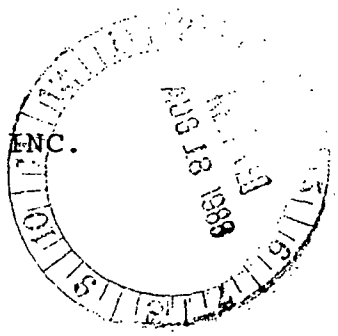
A copy of the production record for Control #00755C which was manufactured August 16-17, 1988 is submitted for your review.

If you require any additional information, please do not hesitate to contact us.

Sincerely,

DANBURY PHARMACAL, INC.

Nessim Maleh FOR
President



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