CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63065

CHEMISTRY REVIEW(S)

Manufacturing and Controls Review

Abbreviated Antibiotic Drug Application #63-065

Date of Application: August 27, 1988
Date of Receipt: August 30, 1988

Date of Correspondence: August 17, 1988
Date of Receipt: August 18, 1988

Date of A-001: October 6, 1988
Date of Receipt: October 14, 1988

Date of A-002: December 15, 1988
Date of Receipt: December 27, 1988

Date of A-003: January 19, 1989
Date of Receipt: January 23, 1989

Date of A-005: February 23, 1989
Date of Receipt: February 24, 1989

Applicant: Danbury Pharmacal, Inc.
131 West Street
P.O. Box 296
Danbury, CT 06813

Product: Minocycline Hydrochloride Capsules, USP, 100 mg

Product is eligible for marketing under 21 CFR 446.160b.

1. Labeling

Container labels - satisfactory for 50's, 100's and 500's.

Package Insert - unsatisfactory. The insert is not the same as Lederle's Minocin (3/88).

2. Manufacturing site: Danbury Pharmacal, Inc.
12 Stoneleigh Avenue
Carmel, NY 10512

3. Description of facility and equipment - satisfactory.

4. Components/Composition

Ingredient	Amount
Minocycline as Minocycline Hydrochloride, USP	100 mg
Starch, NF	mg
Magnesium Stearate	mg
	mg

The applicant obtains minocycline hydrochloride (bulk) from (neither are FDA approved sources).

Production batch sizes capsules, capsules and capsules.

5. Raw material controls - satisfactory.
   Minocycline hydrochloride - satisfactory. The specifications include the revisions published in the Federal Register on August 26, 1988, pages 32606-32610.
   Starch, NF - satisfactory.
   Magnesium Stearate, NF - satisfactory.

6. Finished product specifications - unsatisfactory. The specifications do not include the revisions published in the Federal Register on August 26, 1988, pages 32606 - 32610.

7. Consulting laboratories

8. Master formula records for batches of capsules, capsules and capsules - satisfactory.

9. Manufacturing instructions - unsatisfactory. The application did not contain an adequate explanation for step of the manufacturing instructions under Adjustment.

10. Container/closure system - satisfactory.
The applicant intends to market the drug product in bottles of 50, 100 and 500 capsules.
The bottles are composed of high density polyethylene
resin). The manufacturer of the bottles is

The capacities are mL, mL and mL.
The closures are composed of tinplate. The sizes are 33mm, 38mm and 53mm. The manufacturer is

The liner is composed of a cap liner;

Container/closure controls - satisfactory.

11. Batch records #01218C capsules bulk)
#01219C capsules bulk)
#00755C capsules bulk)

12. Stability Testing Protocol - satisfactory.
Stability Commitment - satisfactory.
Stability Data - complete data has not been submitted.

Expiration Dating Period - cannot be determined at this time due to the lack of stability data.

13. Exhibit samples - sent to FDA laboratory on January 24, 1989.

14. Bioequivalence - satisfactory. See letter to applicant dated March 29, 1989 and Bioequivalence review dated March 16, 1989.

Recommendation - The application is not approvable at this time due to the following deficiencies:

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 % 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).

/S/

John M. Singer 4/10/89

1. CHEMIST'S REVIEW NO. 2

2. AADA # 63-065 NOV 8

3. NAME AND ADDRESS OF APPLICANT
Danbury Pharmacal, Inc.
131 West St.
P.O. Box 296
Danbury, CT 06813

4. AF NUMBER
21 CFR 446.160(b)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Minocycline Hydrochloride

7. NONPROPRIETARY NAME
Minocycline Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

A. Request for waiver on bio batch - Aug. 17, 1988
B. Original submission - August 27, 1988
C. Amendment #001 - Bio study submission - Oct. 6, 1988
D. Amendment #002 - Stability data - Dec. 15, 1988
E. Amendment #003 - Additional exhibit batch data - Jan. 19, 1989 - added as additional bulk supplier
F. Amendment #005 - Additional stability data (no #004) - Feb. 23, 1989
G. Amendment #006 - Dissolution test spec. - Mar. 29, 1989
H. Amendment #007 - Revised labeling etc. - April 18, 1989
I. Amendment #008 - Additional stability data - April 10, 1989
J. Amendment #009 - Final printed labels - Oct. 4, 1989
K. Amendment #010 - Authorization letter - Oct. 31, 1989
L. Amendment #011 - Additional batch data - Nov. 27, 1989 - Made from bulk
M. Amendment #012 - Additional stability data - Jan. 18, 1990
N. Amendment #013 - Additional stability data - April 25, 1990
O. General Correspondence - July 19, 1990
P. Amendment #014 - Deleted 50 mg capsules from package insert Oct. 29, 1990

FDA:

A. Acknowledgement and major deficiency notice - Sept. 11, 1988
B. Request for ADB sample evaluation - Jan 24, 1989
C. Bioequivalency report - Mar. 29, 1989
D. Chem. Review #1-major deficiencies - April 13, 1989
E. ADB report - March 12, 1990

10. PHARMACOLOGICAL CATEGORY
Antibacterial

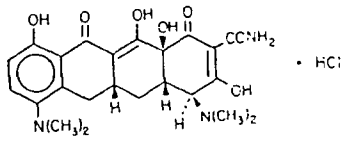
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
AADA - LOA - Amendment #3, Exhibit 4 - Approved May 31, 1990
AADA - unapproved pp. 154-156
DMF · Reviewed 6/15/89 (N.Gregory), deficiencies answered 6/22/89.
DMF · Reviewed 12/8/89 (J.Timper), satisfactory answer on 1/3/90.
DMF Reviewed 2/1/90 (J.Timper), satisfactory

13. DOSAGE FORM
Capsule

14. POTENCY
100 mg

15. CHEMICAL NAME AND STRUCTURE
[4s-(4∝,4a∝,5a∝,12a∝)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxy-2-napthacene carboxamide monohydrate hydrochloride



17. COMMENTS

Applicant petitioned for a waiver of the requirement for minimum batch size of dosage units due to limited availability of bulk minocycline. Although this waiver is not dealt with explicitly in the file, publication of the favorable review of applicant's bioequivalence study implies acceptability. The bioequivalence study was sent as Amendment #001 on Oct. 6, 1988.

Amendment #002 was in response to deficiency letter of Sept. 14, 1988 and contained commitments to supply additional batch data and stability data when available. Amendment #003 contained exhibit samples and batch records for the second and third batches of minocycline and added as a bulk supplier. There is no Amendment #004 in the file. Amendment #005 contained additional stability data on the second and third exhibit batches. Amendment #006 responded to Agency letter requesting incorporation of dissolution testing into the manufacturing controls and stability program. Amendments #007 and #008 responded to the deficiencies outlined in an Agency letter issued following the first comprehensive chemistry review:

A. package insert labeling was revised.
B. applicant withdrew batch sizes of capsules and stated that batch sizes of no greater than capsules will be made. Supplemental submissions will be made for larger sized batches.
C. An in-house specification for finished drug product was included.
D. Stability data on additional two batches was included.

Amendment #009 contained copies of final printed package insert labeling, Amendment #010 added as a contract testing laboratory, and Amendment #011 contained data generated from an additional exhibit batch prepared from bulk minocycline. Amendments #012 and #013 contained additional stability data on this new added batch and, finally, Amendment #014 contained a revised package insert to conform with recommendations in the recent labeling review.

18. CONCLUSIONS AND RECOMMENDATIONS

The bioequivalency study was run on capsules prepared from bulk minocycline, a supplier as yet unapproved. An approved supplier was added in Amendment #003 and comparative dissolution data and stability data submitted with Amendment #011. However, unless additional data is received establishing the bioequivalency of dosage form prepared from bulk, this application cannot be approved until bulk minocycline AADA is approved.

This application is not approvable.

19. REVIEWER: Richard C. Adams /S/ 11/8/90

DATE COMPLETED: 11/5/90

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pages of trade

secret and/or

confidential

commercial

information

Chem Review #2

ANDA Approval Summary

63-065
ANDA Number

Danbury Pharmacal, Inc.
Applicant Name

Minocycline HCl
Established Name of Drug

Capsules
Dosage Form

100 mg
Strength

50's, 100's, 500's
Container size(s)

	Date found Satisfactory	Comment
Labeling	11/13/91	refer to labeling worksheet
Chemistry	11/18/91	refer to chem Review # 3
GMP's		
Manufacturer - Finished Dosage Form	_____	_____
Outside Facilties	_____	_____
Manufacturer(s) - Active Ingredient(s)	_____	_____

/S/ 11/19/91
Chemist Reviewer Date

/S/ 11/19/91
Branch Chief Date

Petition Required ✓ No ___ Yes

Listed Drug Information 505 (j)(2)(A) NOT Required but from Cites, MINO Cardinal

Patent Certification 505(j)(2)(B) N/A TITLE II Drug

Date Patent/Exclusivity Expires (if applicable) N/A _____

Bioequivalence Section

Dissolution Required? ___ No ✓ Yes : ✓ DB ___ DGD 3/29/84 our letter see 3/16/84 bio review

In vivo study(s) required? ___ No ✓ Yes also bio review of 8/22/91 (to new Source of ac

Study(s) Found Acceptable 3/29/84 our letter see 3/16/84 bio review

Waiver Request Granted _____ _____

Total Bioequivalence Requirement Met 8/22/91 _____

/S/ 11/20/91

Administrative Reviewer Date

Approved _____

Disapproved _____

_____ _____

Director, Division of Chemistry Date

Comments:

1. CHEMIST'S REVIEW NO. 3

2. AADA # 63-065

3. NAME AND ADDRESS OF APPLICANT
Danbury Pharmacal, Inc.
131 West St.
P.O. Box 296
Danbury, CT 06813

4. AF NUMBER
21 CFR 446.160(b)

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7. NONPROPRIETARY NAME
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I. Amendment #008 - Additional stability data - April 10, 1989
J. Amendment #009 - Final printed labels - Oct. 4, 1989
K. Amendment #010 - Authorization letter - Oct. 31, 1989
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N. Amendment #013 - Additional stability data - April 25, 1990
O. General Correspondence - July 19, 1990
P. Amendment #014 - Deleted 50 mg capsules from package insert Oct. 29, 1990

*Q. Biostudy on capsules prepared from bulk minocycline - April 5, 1991
*R. Response to 3/28/91 labeling review - May 17, 1991.
*S. Amendment submitted in response to telecons - Oct. 15, 1991
*T. Amendment with FPL - Nov. 1, 1991

*Amendments being reviewed

FDA:

A. Acknowledgement and major deficiency notice - Sept. 11, 1988
B. Request for ADB sample evaluation - Jan 24, 1989
C. Bioequivalency report - Mar. 29, 1989
D. Chem. Review #1-major deficiencies - April 13, 1989
E. ADB report - March 12, 1990
F. Telecon - Oct. I8, 19, 1990
G. EER update - Oct. 18, 1990
H. Telecon - Oct. 25, 1990
I. Chem. Review #2 - minor deficiencies - Nov. 8, 1990
J. Deficiency letter - minor amendment required - Nov. 9, 1990
K. Deficiency letter to firm regarding labeling deficiencies - Mar. 28, 1991
L. Telecon - clarification of remaining issues with all four of this firm's minocycline applications - May 22, 1991
M. Telecon - Oct. 28, 1991
N. Telecon re: labeling - Oct. 29, 1991
O. Telecon re: labeling - Nov. 13, 1991
P. Preapproval inspection request - Nov. 13, 1991

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

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DMF - Reviewed 2/1/90 (J.Timper), satisfactory

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Capsule

14. POTENCY
100 mg

15. CHEMICAL NAME AND STRUCTURE
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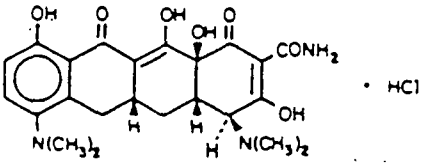

17. COMMENTS

The only outstanding issues identified in Chemistry review #2 (Nov. 8,1990) and the last labeling review (Mar. 28, 1991) were dealt with in amendments submitted, respectively, on April 5, 1991 and November 1, 1991.

Applicant submitted bioavailability data on capsules made from bulk made by an approved supplier. This was found acceptable in a review by the Division of Bioequivalence published on August 22, 1991.

FPL submitted by applicant on November 1, 1991 was found acceptable by J. Phillips on November 13, 1991.

EER updates were requested on October 18, 1990 and November 13, 1991.

18. CONCLUSIONS AND RECOMMENDATIONS

Pending acceptable EER update, this application is approvable.

19. REVIEWER: Richard C. Adams

DATE COMPLETED: 11/13/91

AADA #63-065 /S/ 11/18/91
RAdams
JHarrison /S/ 11/18/91