CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63065/S14, S15

CHEMISTRY REVIEW(S)

ANDA 63-065/S-014, 015

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

PURPOSE OF AMENDMENT/SUPPLEMENT
Firm filed these submissions for an additional dosage strength of 75 mg and the associated labeling changes. 50 mg and 100 mg are approved; a suitability petition for this strength was filed on 1/23/98 and approved 5/26/98, Docket No. 98P-0042/CPI

DATE(S) OF FIRM'S SUBMISSION AND FDA documents:

1.	Original submission	7/31/98
2.	New correspondence correcting an error in #1	8/3/98
3.	Labeling review: minor comments, request for FPL	9/14/98
4.	Additional dissolution data	11/5/98
5.	Division of Bioequivalence review of request for waiver: not acceptable due to integrity problem with original biostudy 11/5/98	
6.	Letter to firm stating that the integrity of the data generated in the biostudy is not reliable...	11/10/98
7.	GC from firm stating that they intend to perform requisite biostudy as required by our letter of 11/10/98.	12/8/98

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Antibacterial	N/A	Minocycline HCl

DOSAGE FORM	POTENCY	RX OR OTC
Capsules	100 mg	℞

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
see below
ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
N/A

PACKAGING
N/A

STABILITY
n/a

REMARKS AND CONCLUSION
Firm filed these submissions for an additional dosage strength of 75 mg and the associated labeling changes. 50 mg and 100 mg are approved; a suitability petition for this strength was filed on 1/23/98 and approved 5/26/98, Docket No. 98P-0042/CPI.

In this time frame problems were being addressed associated with the fact that the biostudy was performed using drug substance supplied by In a letter dated March 9, 1998, the problems were detailed that had ensued with DPI's ANDAs for Minocycline HCL capsules due to the bulk drug substance supplied by The supporting AADA from was withdrawn and drug substance was withdrawn from the market due to serious data integrity questions with DPI had originally submitted data generated from an exhibit batch made from drug substance supplied by Because was approved before DPI withdrew the data package generated from drug substance in order to replace it a submission of exhibit batch and associated data made from drug substance.

OGD had communicated to DPI that because of the data integrity problems with they should resubmit data based upon drug substance, since the data package from drug substance supplied by was withdrawn prior to approval. A preliminary evaluation by OGD of the data submitted to support the approval of your drug product utilizing the drug substance manufactured by indicated that it was acceptable. However, an audit of the in vivo bioequivalence study was necessary because it was performed at under the supervision of , an individual that had been debarred.
The DSI audit found that the integrity of data generated in Study

8409A drug substance) is questionable due to the many errors and non-compliant practices involved in the conduct of the study. Therefore, it was concluded that the study data are not reliable. The Agency's letter of 11/10/98 communicated these facts to DPI and stated that they must repeat a biostudy using the drug substance from or the current supplier, which is approved as an alternate supplier on 4/7/98.

DPI responded that such a study would be done and expected to submit the results by 2/99.

Assuming a favorable result from the above, the data already submitted in support of CMC issues may then be retroactively characterized as free from integrity concerns.

The firm manufactured a batch of 75 mg capsules from drug substance and a control batch of 100 mg capsules using the same equipment at the same facility. The strengths are dose proportional.

CMC data submitted in support of the proposed new strength are:

1. Comparative dissolution profiles.

2. Listing of components demonstrating that the components are the same for all three strengths.

3. Raw material controls, COA's from the vendors and DPI, for all actives and inactives.

4. Executed batch records for the exhibit batch.

5. Testing results for the exhibit batch.

6. Acceptable stability data generated on the exhibit batch.

This supplement is approvable from a CMC standpoint. Submission and signoff by Division of Bioequivalence on the biostudy as discussed in our November 11, 1998 letter, along with resolution of labeling issues, will allow approval of this supplement.

CMC acceptable, approval pending receipt and approval of biostudy.

RECALLS	Reviewer	Date Completed
N/A	R.C.Adams	2/12/99

cc: ANDA 63-065/S-014
Division File
Field Copy

Endorsements:

HFD-643/RAdams/2/12/99 o c.adams, 3/2/99
HFD-643/M.Shih/2/17/99 /S/ for 3/2/99

ANDA 63-065/S-014, 015

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PURPOSE OF AMENDMENT/SUPPLEMENT
Firm filed these submissions for an additional dosage strength of 75 mg and the associated labeling changes. 50 mg and 100 mg are approved; a suitability petition for this strength was filed on 1/23/98 and approved 5/26/98, Docket No. 98P-0042/CPI

DATE(S) OF FIRM'S SUBMISSION AND FDA documents:

1.	Original submission	7/31/98
2.	New correspondence correcting an error in #1	8/3/98
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7.	GC from firm stating that they intend to perform requisite biostudy as required by our letter of 11/10/98.	12/8/98
8.	Not approvable letter for S-014/S-015 referencing need for submission of requested bio study/labeling issues	3/2/99
9.	Submission of biostudy (S-017) approved 5/26/99 RCA	3/3/99
10.	Amendment in response to 3/2/99 deficiency letter	4/5/99
11.	Telephone amendment (response to Bio question)	4/13/99
12.	Review of biostudy for 100mg (and waiver for 75 mg) acceptable	4/13/99

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Antibacterial	N/A	Minocycline HCl

DOSAGE FORM	POTENCY	RX OR OTC
Capsules	100 mg 75 mg 50 mg. RCA	℞

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
see below

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
N/A

PACKAGING
N/A

STABILITY
n/a

REMARKS AND CONCLUSION
Firm filed these submissions for an additional dosage strength of 75 mg and the associated labeling changes. 50 mg and 100 mg are approved; a suitability petition for this strength was filed on 1/23/98 and approved 5/26/98, Docket No. 98P-0042/CPI.

In this time frame problems were being addressed associated with the fact that the biostudy was performed using drug substance supplied by . In a letter dated March 9, 1998, the problems were detailed that had ensued with DPI's ANDAs for Minocycline HCL capsules due to the bulk drug substance supplied by The supporting AADA from was withdrawn and drug substance was withdrawn from the market due to serious data integrity questions with DPI had originally submitted data generated from an exhibit batch made from drug substance supplied by Because was approved before DPI withdrew the data package generated from drug substance in order to replace it a submission of exhibit batch and associated data made from drug substance.

OGD had communicated to DPI that because of the data integrity problems with they should resubmit data based upon drug substance, since the data package from drug substance supplied by was withdrawn prior to approval. A preliminary evaluation by OGD of the data submitted to support the approval of your drug product utilizing the drug substance manufactured by indicated that it was acceptable. However, an audit of the in vivo bioequivalence study was necessary because it was performed at under the supervision of , an individual that had been debarred.

The DSI audit found that the integrity of data generated in Study 8409A drug substance) is questionable due to the many

errors and non-compliant practices involved in the conduct of the study. Therefore, it was concluded that the study data are not reliable. The Agency's letter of 11/10/98 communicated these facts to DPI and stated that they must repeat a biostudy using the drug substance from or the current supplier, which is approved as an alternate supplier on 4/7/98.

DPI responded that such a study would be done and expected to submit the results by 2/99.

The study was filed as S-017, 3/3/99, and approved in a 4/13/99 Division of Bioequivalence review.

The firm manufactured a batch of 75 mg capsules from drug substance and a control batch of 100 mg capsules using the same equipment at the same facility. The strengths are dose proportional.

CMC data submitted in support of the proposed new strength are:

1. Comparative dissolution profiles.

2. Listing of components demonstrating that the components are the same for all three strengths.

3. Raw material controls, COA's from the vendors and DPI, for all actives and inactives.

4. Executed batch records for the exhibit batch.

5. Testing results for the exhibit batch.

6. Acceptable stability data generated on the exhibit batch.

This supplement is approvable from a CMC standpoint. Submission and signoff by Division of Bioequivalence on the biostudy was accomplished by virtue of the 3/3/99 submission (S-017), reviewed and found acceptable in a 4/13/99 review.
S-014 is approvable, S-015 pending labeling review.

RECALLS	Reviewer	Date Completed
N/A	R.C.Adams	5/18/99

cc: ANDA 63-065/S-014
Division File
Field Copy

Endorsements:

HFD-643/RAdams/5/18/99 /S/ 6/2/99
HFD-643/M.Shih/5/19/99 /S/ 6/1/99