

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

65-005

APPLICATION NUMBER:

CORRESPONDENCE



GLOBAL

Global
Pharmaceutical
Corporation

Castor & Kensington Aves.
Philadelphia, PA 19124-5694
Phone: 215-289-2220
Fax: 215-289-2223
E-mail: globalphar@aol.com

December 30, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773

FPL
NDA 031E AMENDMENT
Am

Re: MINOCYCLINE HYDROCHLORIDE, USP
CAPSULES, 50mg AND 100mg
ANDA 65-005
MINOR AMENDMENT

Dear Mr. Sporn:

We are submitting the enclosed minor amendment in response to your fax, dated December 16, 1998 (copy attached). Each deficiency for information is re-iterated, followed by our response in bold type. This amendment covers all four (4) points in addition to corrections pursuant to the labeling deficiencies which were noted in the same correspondence.

We trust that submission of this information will facilitate the review of our application. If there are any questions, please contact me at 215 - 289-2220, ext. 308.

Very truly yours,

Marc M. Feinberg
Vice-President of Quality and Regulatory Affairs

MMF:kcm

Enclosure

cc: Mark Anderson - Project Manager
Debra Pagano -- Philadelphia District

RECEIVED
JAN 27 1999
GEN. REG. DIV.

Medusa

DEC 16 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: #65-005
APPLICANT: Global Pharmaceutical Corporation
DRUG PRODUCT: Minocycline Hydrochloride Capsules, USP,
50 mg and 100 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. It is noted that there is no specification for "Organic Volatile Impurities" in the bulk drug substance as required by USP 23 <467>. Please comment.
2. Regarding the method validation protocol for the Assay and Content Uniformity Assay, we suggest you perform the complete method validation (including robustness, linearity and ruggedness of the method) to demonstrate the adequacy of the method.
3. Please explain the low yield of Exhibit Lot PF117: capsules were obtained from an expected theoretical yield of capsules. What is your acceptable yield range?
4. We note your in-process blend uniformity limits: of label claim. We recommend the acceptance criteria be (mean of individual test results) with a relative standard deviation (RSD) of 5.0%.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following:

A satisfactory compliance evaluation of your facility is required prior to approval. Please note the Office of Compliance currently considers Global Pharmaceutical Corporation unacceptable based on inspectional observations made during June-July, 1998.

Sincerely yours,



Florence Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

AND #65-005

APPLICANT: Global Pharmaceutical Corp.

DRUG PRODUCT: Minocycline Hydrochloride, ^{uSP} 100 mg & 50 mg Capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



GLOBAL

Global
Pharmaceutical
Corporation

Castor & Kensington Aves.
Philadelphia, PA 19124-5694
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E-mail: globalphar@aol.com

September 16, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773

N/AE

Re: Minocycline Hydrochloride Capsules, USP 50mg & 100mg
ANDA 65-005
LABELING AMENDMENT

Dear Mr. Sporn:

The enclosed changes to the labeling (bottle labels and outsert) are attached as per a request received from Office of Generic Drugs (OGD) on August 6, 1998.

We trust that the labeling we have developed utilizing your comments is acceptable. If there are any questions, however, please contact me directly at (215) 289-2220, ext. 308.

Very truly yours,

Marc M. Feinberg
Vice-President of Quality and Regulatory Affairs

MMF:kcm

Enclosures

RECEIVED

SEP 23 1998

GENERIC DRUGS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

AND #65-005

APPLICANT: Global Pharmaceutical Corp.

DRUG PRODUCT: Minocycline Hydrochloride, 100 mg & 50 mg Capsules

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 20 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: #65-005

APPLICANT: Global Pharmaceutical Corporation

DRUG PRODUCT: Minocycline Hydrochloride Capsules, USP,
50 mg and 100 mg.

The deficiencies presented below represent MAJOR deficiencies.

Chemistry Deficiencies:

1. Regarding the Active Ingredient:
 - a. We note that no specifications are given for the in-house testing for Bulk Density, Tap Density and Particle Size. Please explain.
 - b. Please include "Description" as one of the test requirements for the bulk material.
2. Regarding the Composition Statement:
 - a. The active ingredient should be stated as "Minocycline Hydrochloride USP" instead of "Minocycline USP". There is no "Minocycline USP".
 - b. The quantitative composition statement should be expanded to reflect the proposed maximum production batch size.
 - c. Please provide a list of the ingredients contained in the capsule shells.
3. On page 12 0002, it is stated that approximately capsules of 100 mg were manufactured. It is stated capsules in the rest of the application. Please revise.
4. It is not clear if there are any in-process tests being performed before encapsulation, except checking final blend yield and reconciling. Please comment or clarify.

5. Regarding the batch records:
- a. It is not clear how you obtained the calculations for Minocycline HCl (page 3 of 16) for the two pilot batches. What is the procedure for selecting bulk lots when more than one batch of bulk is needed?
 - b. We note there was a time lag between blending and encapsulation for the two pilot lots. Please provide a time frame and procedures for handling the blend during the holding period once production of commercial size batches occurs.
6. Please explain why testing of "Impurities/Degradants" is not included for finished product release specification.
7. Specifications under Post Approval Commitments on page 17 0009 do not include testing for "Impurities/Degradants". Please clarify why the Specifications listed on page 17 0006 are different from the ones provided on page 17 0009.
8. A signed statement should be provided to certify that the manufacturing site complies with all of federal and local environmental laws and regulations.

Sincerely yours,



Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

ANDA 65-005

Global Pharmaceutical Corporation
Attention: Marc M. Feinberg
Castor & Kensington Avenues
Philadelphia, PA 19124

FEB 26 1998

|||||

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated February 19, 1998 and your correspondence dated February 20, 1998.

NAME OF DRUG: Minocycline Hydrochloride Capsules USP, 50 mg and 100 mg

DATE OF APPLICATION: January 16, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 21, 1998

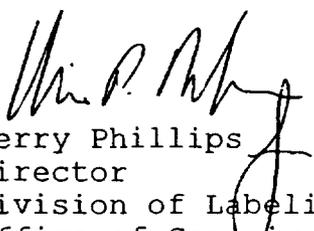
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,


Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



GLOBAL

Global
Pharmaceutical
Corporation

January 16, 1998

Castor & Kensington Aves.
Philadelphia, PA 19124-5694
Phone: 215-289-2220
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E-mail: globalphar@aol.com

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773

Re: Abbreviated New Drug Application
Minocycline hydrochloride
50 and 100 mg Capsule.

Dear Mr. Sporn:

We are submitting the attached Abbreviated New Drug Application for Minocycline hydrochloride capsules, 50 mg and 100 mg, in accordance with new drug regulations, 21 CFR Section 314.94. The reference drug product is MINOCIN® Minocycline HCl pellet filled capsules, 50 mg and 100 mg, manufactured by Lederle Laboratories.

This ANDA submission consists of seven volumes. If there are any questions or comments, please contact me directly at 215-289-2220, extension 308.

Very truly yours,

Marc M. Feinberg
Vice-President of Quality and Regulatory Affairs
Global Pharmaceutical Corporation

MMF:kcm

cc: Field copy – Debra Pagano,
Pre-Approval Manager, Philadelphia District

RECEIVED

JAN 21 1998

GENERIC DRUGS



GLOBAL

Global
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Castor & Kensington Aves.
Philadelphia, PA 19124-5694
Phone: 215-289-2220
Fax: 215-289-2223
E-mail: globalphar@aol.com

February 20, 1998

NEW CORRESP

NC NAT
2/24/98
[Signature]

Mr. Gregg Davis
Office of Generic Drugs
US FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773

Fax 301-594-1174

RE: Minocycline HCl Capsules,
50 mg and 100 mg, USP
ANDA 65 - 005

Dear Mr. Davis:

Pursuant to our telephone conversation on February 19, 1998, regarding our filed ANDA for Minocycline HCl Capsules, I have enclosed the following:

- The issue raised by the Division of Bioequivalence regarding a need for a "Food Study"

We would submit that previous correspondence from that division advised that a "fasting study" is sufficient for generic Minocycline Capsules. Our contract laboratory, [redacted], contacted that division (see attached correspondence) prior to initiating our Bio-study.

- Will there be a scale-up from the pilot batch size? If so, representative copies of the proposed batch production must be submitted.

The batch size "scale-up" would be increased from that reported in the pilot batches PF-117 (125,000 capsules) and PF 129 [redacted]. The maximum batch size we expect to manufacture is [redacted] capsules. Copies of the proposed batch production records are enclosed as 11 0037 - 11 0066.

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FEB 23 1998

GENERIC DRUGS



February 20, 1998
Page 2

- Are there GMP/GLP compliance certifications for _____ s and _____ ?

The GMP/GLP compliance certification for _____ is enclosed (Exhibit 03 0008), it was accidentally omitted from the submission. The GMP/GLP Certification from _____ :c. was incorrectly listed as page 06 0009. It should be changed to pages 06 0007 and 06 0510. Copies of these pages are attached.

- There should be the actual Certificates of Analyses by Global Pharmaceutical Corp for the active drug substance.

The actual testing results of the active drug product, Minocycline hydrochloride are enclosed as exhibits 08 0008 A/B and 08 0008 C/D. Two lots of raw material were used in the manufacture of the pilot lots.

- There must be a "reprocessing statement" in the ANDA.

The "Reprocessing Statement" is on page 11 0003. It does not however, implicitly state "reprocessing" but states "Changes in these procedures will be reported in accordance with 21CFR314.70". I have however, added an additional section entitled "Reprocessing" which would become part of Section XI, Part 3.

Sincerely,

Marc M. Feinberg
Vice-President of Quality and Regulatory Affairs

MMF:kcm

CC: D. Pagano, PHI-DO (PAI)



GLOBAL

Global
Pharmaceutical
Corporation

Castor & Kensington Aves.
Philadelphia, PA 19124-5694
Phone: 215-289-2220
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May 29, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773

ORIG AMENDMENT
N/A/C

RE: MINOCYCLINE HYDROCHLORIDE, USP
Capsules, 50mg and 100mg
ANDA 65 005
MAJOR AMENDMENT

Dear Mr. Sporn:

We are submitting the enclosed amendment in response to your letter of May 20, 1998, (copy attached). Each request for information is reiterated in bold type, followed by our response. This amendment covers all points 1 through 8 of your letter.

We trust that submission of this information will facilitate the review of our application. If there are any questions, however, please contact me at (215) 289-2220.

Very truly yours,

Marc M. Feinberg

Marc M. Feinberg
Vice-President of Quality and Regulatory Affairs

MMF:kcm

Enclosure

cc: Mark Anderson
Debra Pagano - Philadelphia District

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JUN 03 1998

GENERIC DRUGS

1. Regarding the Active Ingredient:

- a. We note that no specifications are given for the in-house testing of Bulk Density, Tap Density and Particle Size. Please Explain.**

The raw material supplier had not provided specifications for Bulk Density, Tap Density and Particle Size. We have examined several lots of raw material and set the following specifications:

Bulk Density -
Tap Density -
Particle Size - sieve

These specifications were communicated to our raw material supplier who has agreed that their manufacturing process will yield an active pharmaceutical ingredient that should meet our established specification. These specifications have been added to our laboratory testing sheets.

- b. Please include "Description" as one of the test requirements for the bulk material.**

We have included "Description" to our analytical testing specifications for the active ingredient. Copies of revised specifications are attached (see Attachment A).

2. Regarding the Composition Statement:

- a. The active ingredient should be stated as "Minocycline Hydrochloride USP" instead of "Minocycline USP". There is no "Minocycline USP".**

We have changed the listing of the active ingredient to "Minocycline HCl, USP (equivalent to _____mg Minocycline anhydrous). This is in accordance with the USP Monograph that states "Minocycline Hydrochloride Capsules contain the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of minocycline (C₂₃H₂₇N₃O₇). This change was made on our composition statement (see Attachment B).

- b. The quantitative composition statement should be expanded to reflect the proposed maximum production batch size.**

The quantitative composition statement has been expanded to reflect the proposed maximum batch size _____ capsules. We have enclosed a revised page 07 0003 (see Attachment B) to incorporate this addition.

- c. Please provide a list of the ingredients contained in the capsule shells.**

The composition of the capsule shells is listed as a continuation of Point 2 Quantitative Composition, Statement of Composition (c), page 07 0003A (see Attachment C).

- 3. On page 12 0002, it is stated that approximately _____ capsules of 100mg were manufactured. It is stated _____ capsules in the rest of application. Please revise.**

The _____ capsules was a typographical error. The amount has been changed to correct figure of _____ capsules. A copy of the revised page 12 0002 is enclosed (see Attachment D).

4. **It is not clear if there are any in-process tests being performed before encapsulation, except checking final blend yield and reconciling. Please comment or clarify.**

Although not stated, Global conducts extensive in-process blend uniformity testing prior to encapsulation. This testing during our validation batches includes thief sampling from a minimum of ten blender positions and ten thieved samples from various drum locations. Enclosed is a diagram which indicates the sampling positions. Additionally, Global commits to conducting blend uniformity testing on ten in-process samples for routine production batches. This testing plan will continue until enough data is generated to propose the elimination of the practice. The batch production records have been changed to include this action and an additional worksheet has been added to the batch production record (see Attachment E).

5. Regarding the batch records:

- a. It is not clear how you obtained the calculation for Minocycline HCl (page 3 to 6) for the two pilot batches. What is the procedure for selecting bulk lots when more than one batch of bulk is needed?**

The pilot batch, PF-129 utilized two batches of bulk active. The batch production record (page 3 of 6) refers to Memorandum dated August 7, 1997. This "Memo" was inadvertently missed during the photocopying of the batch production record. A copy of the referenced memo is enclosed (see Attachment F).

Global Pharmaceutical Corporation follows ' when selecting the bulk lots to be utilized. This practice is referenced in SOP "Selection of Batch Materials, Packaging Components and Finished Product for Use or Distribution A copy of the SOP is enclosed (see Attachment G).

- b. We note there was a time lag between blending and encapsulation for the two pilot lots. Please provide a time frame and procedures for handling the blend during the holding period once production of commercial size batches occurs.**

The production of all products with respect to any "lag time" is governed by SOP (see Attachment H). The cumulative time for all steps in the production of tablets and capsules is would point-out that the lag time from blending to encapsulation of the two pilot lots was for PF-117 less than and PF-129 less than The blending of PF-129 was completed on a Friday with the encapsulation starting on the subsequent Monday.

6. Please explain why testing of "Impurities/Degradants" is not included for Finished Product Release Specifications.

We agree that the finished drug product testing should include "Impurities/Degradants". Our finished product release specifications has been changed to include the testing of Impurities/Degradants (see Attachment I).

7. Specifications under Post Approval Commitments on page 17 0009 do not include testing for Impurities/Degradants". Please clarify why the Specifications listed on page 17 0006 are different from the ones provided on page 17 0009.

It was initially thought that we would test for "Impurities/Degradants" only during the accelerated stability period. We will now test the finished product at accelerated and control room temperature stability periods for the Impurities/Degradants". As previously stated in item #6, we will include "Impurities/Degradants" testing as part of finished product release. We have made corrections to pages 17 0006, 17 0007, 17 0009 and 17 0010. The revisions are enclosed.(see Attachment J).

- 8. A signed statement should be provided to certify that the manufacturing site complies with all of federal and local environmental laws and regulations.**

A copy of our environmental compliance certification is enclosed as page 20 0003(see Attachment K).