CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-019

ADMINISTRATIVE DOCUMENT(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : December 12, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 12-DEC-2001

SUBJECT: Examination of the request for waiver submitted with an ANDA for Deferoxamine Mesylate Injection, 500 mg/Vial **(the 2 g/Vial is a new strength submitted as an amendment)** to determine if the application is substantially complete for filing.

Abbott Laboratories has submitted ANDA 76-019 for Deferoxamine Mesylate Injection, 500 mg/Vial **and (2 g/Vial as a new strength submitted as an amendment)**. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must ~~formally~~ review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by ~~Amide~~ Abbott on November 7, 2001 for its Deferoxamine Mesylate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

✓ Waiver meets statutory requirements 12/18/2001

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence 1/17/02 Date

Palat, Cuthbert (Ted)

To: CDER-DDR600
Cc: Warren, Nadine; Smith, Glen J
Subject: ANDA 76-019

Folks,

Please close out the July 1, 2003 submission. The Close date should be July 23, 2003. The Division responded to the Firm correspondance on July 23, 2003. I have tabbed the fax with a blue tab. I will bring the jacket along with a copy of this email to your office.

LCDR Ted Palat, PharmD
Office of Generic Drugs, CDER, FDA
7500 Standish Place, MPN II
Rockville, MD 20855
301-594-0338

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-019

CORRESPONDENCE

meB

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

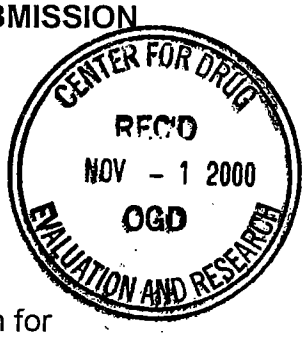
505(j)(2)(A) OK
09-DEC-2000
Gregory S. Davis

October 31, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Acting Director

ELECTRONIC SUBMISSION ENCLOSED



Re: **Deferoxamine Mesylate for Injection USP, 500 mg/vial**
Original Abbreviated New Drug Application

Abbott Laboratories hereby submits an Abbreviated New Drug Application for Deferoxamine Mesylate for Injection USP, 500 mg/vial, in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act. The subject drug is a prescription drug and not an over-the-counter drug.

Deferoxamine Mesylate for Injection USP is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 20th Edition, page 3-99. A copy appears in Section II.

The active ingredient, indications (applicable to the injection), route of administration, dosage form, and strength for Deferoxamine Mesylate for Injection USP are the same as those of the innovator's product, Desferal®, sponsored by Novartis Pharma AG. Comparative information is contained in Section IV.

The labeling is the same in content as that of the reference drug, Desferal®, except for changes that are necessary due to a change in manufacturer. A copy of the innovator's package insert is provided in Section V.

The first three production batches of Deferoxamine Mesylate for Injection USP, 500 mg/vial, will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Our complete stability protocol and post-approval commitments are contained in Section XVII.

For the convenience of the Agency, documentation for Sterilization Process Validation is contained in a separate volume with a dedicated table of contents.

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drugs electronic submission program. A one-page printout of the EVA-compliant export log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

Abbott Laboratories hereby certify that we have sent a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call me at (847) 937-3413.

Sincerely,

ABBOTT LABORATORIES

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
FAX: (847) 938-7867

ANDA 76-019

DEC 08 200

Abbott Laboratories, Inc.
Attention: Jonathan P. Dohnalek
Dept. 0389, Bldg. AP30-1
200 Abbott Park Road
Abbott Park, IL 60064-6157

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.

NAME OF DRUG: Deferoxamine Mesylate for Injection USP, 500 mg/vial

DATE OF APPLICATION: October 31, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 1, 2000

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:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

November 7, 2001

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary Buehler
Acting Director

Re: ANDA 76-019 Deferoxamine Mesylate for Injection USP, 500 mg/vial & 2 g/vial

MAJOR AMENDMENT – NEW STRENGTH

INCLUDING RESPONSE TO CHEMISTRY, MICROBIOLOGY, AND LABELING DEFICIENCIES

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the drug product submitted October 31, 2000. We are responding to the Agency's action letter dated May 11, 2001 (chemistry and labeling deficiencies) and June 12, 2001 (microbiology deficiencies).

Additionally, Abbott Laboratories hereby amends the above-referenced pending ANDA to provide for the addition of a new strength of Deferoxamine Mesylate for Injection USP, namely 2 g/vial. The manufacturing and controls sections (including components and composition, test methods, and specifications) and documentation for Sterilization Process Validation for the new 2 g/vial configuration are the same as in our current pending ANDA 76-019. Only the drug product strength (potency), glass container, and ——— are new. The additional new information to support the new 2 g/vial configuration follows the response sections for chemistry, microbiology and labeling deficiencies.

The Agency made the following comments:

Chemistry Deficiencies:

COMMENT: "1. DMF # ——— is not adequate and the firm has been notified of the deficiencies. The application cannot be approved until the DMF deficiencies have been addressed. Also for the ——— your proposed limits for the ——— Residual Solvent and Total Impurities may be too high and should be revised. We also recommend Tests and Specifications for Total Microbial Count and Solution Haze."

CENTER FOR DRUG
NOV 0 8 2001

11-9-01

RESPONSE: We acknowledge that DMF # [redacted] is not adequate and [redacted] has been notified of the deficiencies. We also acknowledge that the application cannot be approved until the DMF deficiencies have been addressed.

Biogal, the holder of DMF # [redacted], has advised us that they have addressed all of the outstanding deficiencies in their DMF # [redacted] for the Drug Substance, Deferoxamine Mesylate USP, in their correspondence of July 2, 2001. Exhibit 1 contains a copy of the cover letter from [redacted]

We have tightened the limit for Acetonitrile Residual Solvent from "NMT [redacted] to "NMT [redacted]". Exhibit 2 contains the revised specification for the Drug Substance. We have also tightened the limit for Total Impurities from "NMT [redacted] to "NMT [redacted]". (Please refer to Exhibit 2.)

Additionally, we have also revised the tests and specifications for the Drug Substance to include the Total Microbial Count (Aerobic Microbial Count) and Solution Haze (Clarity and Opalescence) testing requirements. Please refer to Exhibit 2. The test methods for Aerobic Microbial Count and Clarity and Opalescence are contained in Exhibit 3.

Furthermore, the revised in-house Certificates of Analysis for Deferoxamine Mesylate USP, Lot # 80500100100 and Lot # 80500100200, which were used to manufacture the exhibit batches, are provided in Exhibit 4.

COMMENT: "2. For Product Release, we recommend Tests and Specifications for Identification by [redacted]

RESPONSE: We have revised the Product Release tests and specifications to include Identification by [redacted] Exhibit 5 contains the revised Product Release specification.

The test methods for the Identification by [redacted] are included in Exhibit 6. For [redacted] an alternate visual test method is also included in addition to the preferred instrumental test method.

COMMENT: "3. Also for Product Release, your proposed Impurity Specifications are not supported by the submitted Release Data and may be too high. The [redacted] Impurity did not exceed [redacted], the Single Largest Impurity did not [redacted] and Total Impurities did not exceed [redacted] We recommend revising the Impurity Specifications for Product Release."

RESPONSE: We have tightened the Impurity specifications for Product Release from [redacted] NMT [redacted], other individual NMT [redacted] and total NMT [redacted] to [redacted] NMT [redacted], other individual NMT [redacted], and total NMT [redacted] Exhibit 5 contains the revised Product Release specification.

COMMENT: "4. For Stability Testing, we recommend Tests and Specifications for Identification by [redacted]. We also recommend a Test and Specification for Instrumental Color of Solution."

RESPONSE: We have revised the Stability Protocol to include the test and specification for [redacted]. Exhibit 7 contains the revised Stability Protocol for the drug product.

Additionally, we note that the tests and specifications for Identification by [redacted] are currently included in the Product Release testing requirements. (Please refer to Exhibit 5.) Therefore, we believe that the addition of these identification tests to the Stability Protocol is not necessary since these tests are not considered to be stability indicating tests.

COMMENT: "5. Your Stability Impurity Specifications are not supported by the submitted Stability data and may be too high. The [redacted] Impurity did not exceed [redacted], the Single Largest Impurity did not [redacted] and Total Impurities did not exceed [redacted] We recommend revising the Stability Impurity Specifications."

RESPONSE: Upon complete review of the current stability data for the drug product, we have tightened the Stability Impurity Specifications from [redacted] NMT [redacted], other individual NMT [redacted], and total NMT [redacted]," to "[redacted] NMT [redacted], other individual NMT [redacted], and total NMT [redacted] (Please refer to Exhibit 7.)

Up-to-date 12-month controlled room temperature stability data for exhibit batches are contained in Exhibit 8.

COMMENT: "6. Please commit to perform Reconstituted Stability Testing for Assay and Impurities for the first three production batches."

RESPONSE: We confirm that the current Stability Protocol includes the Reconstituted Stability Testing for Assay and Impurities for the first three production batches and for the annual batches thereafter. (Please refer to page 442 of the original submission and the revised Stability Protocol provided in Exhibit 7 of this submission.)

APPEARS THIS WAY
ON ORIGINAL

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

COMMENT: **"We note that you propose to use an in-house [redacted] Assay method for quantification of Deferoxamine Mesylate. While the use of a properly validated alternate method is acceptable, please be advised that approval to use an analytical procedure that differs from that in the USP does not release your firm from any obligations to comply with the methods and procedures in the USP. You should be aware that USP procedures remain the regulatory method, and results obtained thereof will rule in the event of a dispute."**

RESPONSE: We note and acknowledge that a proposed in-house [redacted] Assay method is utilized for quantification of Deferoxamine Mesylsate. Additionally, we note and acknowledge that while the use of a properly validated alternate method is acceptable, the approval to use an analytical procedure that differs from that in the USP does not release our firm from any obligations to comply with the methods and procedures in the USP. Furthermore, we note and acknowledge that the USP procedures will remain the regulatory method, and results obtained thereof will rule in the event of a dispute.

Redacted 2

Page(s) of trade secret and /or confidential commercial information

Labeling Deficiencies:

1. **CONTAINER – 500 mg/vial**

   a. **Does your proposed container label reflect the true size? To be acceptable as final print, labels must be of actual size, color, and clarity. Please assure that these criteria are met prior to submission of final print.**

   b. **Replace '** [redacted] **' with "Reconstituted Exp.".**

   c. **Include the phrase "For single use only".**

   d. **Include the text "Discard unused portion."**

2. **CARTON**

   a. **See comments under CONTAINER except (b).**

   b. **Revise '** [redacted] **' to read "Usual Dosage".**

   c. **Include a comma after the term "subcutaneous".**

3. **INSERT**

   a. **GENERAL**

      Please note that the labeling for the reference listed drug, Desferal® Injection was last approved on May 25, 2000. The following comments are based on this labeling.

   b. **TITLE**

      We encourage the inclusion of "Rx Only" beneath the title.

   c. **DESCRIPTION**

      i. **...is *N*-[5-3-[(5-Aminopentyl...[note upper case "A"]**

      ii. **Include the molecular formula.**

   d. **INDICATIONS AND USAGE**

      Deferoxamine mesylate for injection is ... [add "for injection"]

e. WARNINGS

i. First paragraph, second sentence:

...acuity including visual loss; impaired peripheral, color, and night vision; and retinal pigmentary abnormalities. The auditory...

ii. First paragraph, last sentence – Revise to read as follows:

[ ]

iii. Penultimate paragraph:

...pretreatment rates. [delete the parenthetical statement]

f. PRECAUTIONS

i. General

A) Second paragraph, first sentence:

...*enterocolitica* infections. In some...

B) Third paragraph – Revise to read as follows:

[ ]

C) Delete all remaining text in this subsection from the fourth paragraph on.

ii. Drug Interactions

Delete this subsection in its entirety.

iii. Information for Patients

Delete the first paragraph

iv. **Pediatric Use**

A) **Delete the first paragraph.**

B) **Second paragraph:**

...established (see INDICATIONS AND USAGE).

g. **ADVERSE REACTIONS**

i. **First item (At the injection site) – Replace with the following text.**

Skin: **Localized irritation and pain, swelling and and induration, pruritus, erythema, wheal formation.**

ii. **Hypersensitivity Reactions and Systemic Allergic Reactions – Revise to read.**

Hypersensitive Reactions**: Generalized ——— (rash), urticaria, anaphylactic reaction.**

iii. **Body as a Whole**

Delete this item in its entirety.

iv. **Hematologic, Musculoskeletal, Nervous system**

Delete these three subsections.

v. **Special Senses – revise to read as follows:**

Special Senses: **Ocular and auditory disturbances (See WARNINGS)**

vi. **Respiratory, Skin, Urogenital**

Delete these three subsections.

vii. **Include the following as the last item.**

h. OVERDOSAGE

i. Signs and Symptoms – Revise to read as follows.

[redacted]

ii. Treatment

A) Delete the second sentence of the first paragraph.

B) Add the following as the new second paragraph.

[redacted]

i. DOSAGE AND ADMINISTRATION

i. Acute Iron Intoxication

A) Intravenous Administration

...SHOULD NOT EXCEED 15 MG/KG/HR. [delete " [redacted]

B) Dosage – Combine the first two paragraph and revise to read as

[redacted]

ii. Chronic Iron Overload – Intramuscular Administration:

A) First sentence:

...Solution above. [delete a comma]

B) Delete the last sentence.

j. **HOW SUPPLIED**

Include the text "For single use only" and "Discard unused portion.".

RESPONSE: We have revised the proposed 500 mg labeling pursuant to your comments in the deficiency fax of May 11, 2001. Please note, however, that the carton and package insert for the referenced listed drug, Desferal ®, was updated and approved by the FDA on April 9, 2001. Pursuant to a telephone conversation between Chan Park, FDA Labeling Reviewer, and Jean Kirkeleit Davis of Abbott on August 22, 2001, we have followed the Agency instructions and revised our carton and package insert according to the newly approved innovator labeling as well as the deficiency letter, with the innovator labeling superceding the deficiency letter.

Final Printed Labeling (FPL) samples are provided for the Container Label, Carton, and Package Insert in Exhibit 11. For ease of review, we have provided side-by-side comparisons for the Container Label, Carton and Package Insert in Exhibits 12.

Please note that the Package Insert includes reference to both the 500 mg and 2 g vials.

APPEARS THIS WAY
ON ORIGINAL

Additional Information:

As previously stated, Abbott Laboratories hereby amends the current pending ANDA 76-019 for the subject drug product submitted October 31, 2000, to provide for an additional new strength of Deferoxamine Mesylate for Injection USP, namely a 2 g/vial. The manufacturing and controls sections (including components and composition, test methods, and specifications) and documentation for sterilization process validation for the new 2 g/vial configuration are the same as in our current pending ANDA 76-019. Only the drug product strength (potency), glass container, and [redacted] are new.

In support of this submission for the new 2 g/vial configuration, the following sections are provided, as they relate to the original ANDA submission table of contents:

Exhibit 13	Section IV & Section V	Comparison between generic and reference listed drug and labeling
Exhibit 14	Section VII.3	Batch size and formula for Deferoxamine Mesylate for Injection USP, 2 g/vial
Exhibit 15	Section VIII.1	Supplier and in-house Certificate of Analysis for Deferoxamine Mesylate USP, Lot # 80500100900, which was used in the manufacture of the exhibit batch. Also included are the [redacted] for the referenced lot of Deferoxamine Mesylate USP. (Please refer to Exhibit 2 of this submission for the drug substance specification.)
Exhibit 16	Section XI.1.c	Solution manufacturing directions overview for the drug product – [redacted] for 2 g/vial
Exhibit 17	Section XI.2	Blank master batch records
Exhibit 18	Section XII	Executed batch records and in-process test results
Exhibit 19	Section XIV.	Summary of container/closure system and components specification and test data
Exhibit 20	Section XV & Section XVI.3	Certificate of Analysis and [redacted] for the finished drug product (Please refer to Exhibit 5 of this submission for the Product Release specification.)
Exhibit 21	Section XVII.4	Stability data summaries (Please refer to Exhibit 7 of this submission for the stability protocol and post-approval stability commitments.)
Exhibit 22	Micro. Vol., Attachment 7	Summary of drug [redacted]

Abbott Laboratories hereby certify that we have sent a true copy of this submission to the Lenexa, Kansas, FDA District Office.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

Jean Kirkeleit Davis
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 935-9873
Fax: (847) 938-7867

ABBOTT

Hospital Products Division
Abbott Laboratories
D-37K, Bldg. J45-2
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

NDE MTB 2-1-02

N/PAC

January 30, 2002

ORIG AMENDMENT

Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Attention: Gary J. Buehler, R.Ph.
Director

Re: ANDA 76-019 Deferoxamine for Injection, USP, 2 g vial

Amendment—New Strength
Requested Information

Abbott Laboratories (Abbott) is amending the above referenced abbreviated new drug application submitted on October 31, 2000. Reference is made to the telephone conversation between Martin Shimer, R.Ph., of the Regulatory Support Branch and Jean Kirkeleit Davis of Abbott on January 22, 2002. Mr. Shimer referred to the amendment to this pending application dated November 7, 2001, which included information concerning the new 2 gram strength of deferoxamine. Mr. Shimer requested the following information be provided prior to the end of the month:

Exhibit I	Basis for ANDA Submission Section II.
Exhibit II	Patent Certification and Exclusivity Statement Section III.
Exhibit III	Bioavailability/Bioequivalence Section VI.
Exhibit IV	Description of the Manufacturing Facility Section IX.
Exhibit V	Reprocessing Statement Section XI. 3.

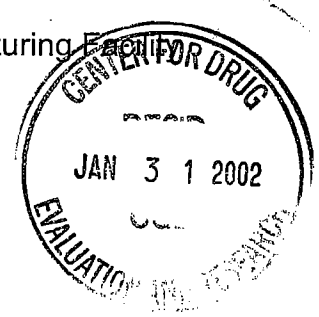


Exhibit VI	DMF Information for Rubber Closure Section XIV. 2. b. NOTE: The same rubber closure is used for both the 500 mg and the 2 g products. The information included in this Exhibit is identical to that which was provided in the original submission dated October 31, 2000.
Exhibit VII	Stability Protocol, Post Approval Commitment and Proposed Expiration Date Section XVII. 1-3. NOTE: Section XVII. 1-2. was provided for both the 500 mg and 2g in the November 7, 2001 amendment as Exhibit 7. However, we are providing the identical information in this submission for ease of review.
Exhibit VIII	Statement Regarding the Availability of Samples Section XIX.
Exhibit IX	Environmental Impact Analysis Statement Section XX.
Exhibit X	GDEA Certifications Concerning Conviction and Debarment
Exhibit XI	Certificate of Analysis—Water for Injection, USP

Abbott certifies that we have provided a true copy of this submission to the Lenexa, Kansas FDA District Office.

Should you have any questions or require additional information, please contact the undersigned.

Sincerely,

ABBOTT LABORATORIES

Jean Kirkeleit Davis

Jean Kirkeleit Davis
Manager, Regulatory Affairs
Hospital Products Division
Phone: 847-935-9873
Fax: 847-938-7867
E-mail: jean.kirkeleitdavis@secure.abbott.com

cc (letter only): M. Shimer, FDA Regulatory Support Branch

ABBOTT

Hospital Products Division
Abbott Laboratories
D-37K, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

ORIG AMENDMENT
N/AF

April 12, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Director

Jeen Min
Project Manager

Re: **ANDA 76-019 – Deferoxamine Mesylate for Injection, USP**
500 mg/vial & 2 g/vial

Revised Final Printed Labeling Amendment

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the drug product submitted October 31, 2000, and amended November 7, 2001.

The reference listed drug for ANDA 76-019 is Novartis' DESFERAL® (deferoxamine mesylate for injection USP) NDA 16-267. Recently, Novartis received approval for NDA 16-267/S-039. This supplement provides for the revision of the Adverse Reactions section of the package insert. A copy of the approval letter received from FDA, containing the package insert is provided as **Exhibit I**. For convenience, we identified the revisions in the right hand margin and drew a box around the changed text.

Abbott Laboratories has updated the package insert submitted in the November 7, 2001 Amendment to include the approved revision to the reference listed drug's package insert. Twelve copies of the final printed label (package insert) are provided as **Exhibit II**. There are no changes to the vial labels or carton labeling.

To facilitate review of this amendment, and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of our proposed labeling with our last submission, with all differences annotated and explained is provided as **Exhibit III.**

RECEIVED
APR 1 5 2002
OGD / CDER

If you require any clarification or further information, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
FAX: (847) 938-7867

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

November 25, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

ATTENTION: Gary J. Buehler, Director
Glenn Smith, Chemistry Team Leader
Jeen Min, Project Manager

Re: ANDA 76-019 – Deferoxamine Mesylate for Injection, USP

Dear Sirs,

This correspondence is in reference to the following comment in the Agency's July 16, 2002 deficiency letter to ANDA 76-019:

> "Review of Adverse Reaction Reports submitted to the Agency has indicated the potential for inflammatory reaction resulting from the use of Deferoxamine. These adverse reactions do not appear to be related to endotoxins and instead may be due to the presence of other agents in the drug substance which can elicit an inflammatory response. Please develop a method for screening your drug substance to prevent this type of adverse reaction and revise your drug substance specifications accordingly."

Abbott Laboratories hereby requests that OGD provide additional information and direction to Abbott sufficient to prepare a complete response to address this deficiency letter.

If you require any clarification or further information regarding this request, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

JDohnalek.

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
FAX: (847) 938-7867

RECEIVED
NOV 26 2002
OGD / CDER

ABBOTT

Hospital Products Division
Abbott Laboratories
D389, Bldg. J45
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

December 20, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

N/AC

ATTENTION: Gary J. Buehler
Director

Re: ANDA 76-019 Deferoxamine Mesylate for Injection, USP, 500 mg/vial and 2 g/vial

AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the drug product submitted October 31, 2000 to provide for the addition of a new [redacted] used in the manufacture of the 2 g/vial presentation of Deferoxamine Mesylate for Injection, USP, at Abbott Laboratories, McPherson, Kansas facility. The same [redacted] (Original ANDA, page 867) will also apply to [redacted] is an [redacted] with a shelf area of [redacted] and [redacted]

The manufacturing and control sections, including components and composition, container/closure system, test methods, and specifications, are the same as in the current ANDA. Only the [redacted] is new.

In support of this submission, the following information is provided:

Exhibit I	Blank master batch records
Exhibit II	Executed batch records
Exhibit III	Certificate of Analysis for the finished drug product
Exhibit IV	Stability data summaries
Exhibit V	Summary of product lyophilization
Exhibit VI	Summary of [redacted]

Abbott Laboratories hereby commits that the first three commercial batches of Deferoxamine Mesylate for Injection, USP, 2 g/vial, manufactured using [redacted] will be placed into our stability program at controlled room temperature (25°C/60% RH) and evaluated at initial, 3, 6, 9, 12, 18 and 24 months. Yearly thereafter, at least one (1) commercial batch of Deferoxamine Mesylate for Injection USP, 2 g/vial, will be added to the stability program. The stability test results will be reported to the Agency as they become available.

Abbott Laboratories hereby certify that we have sent a true copy of this submission to the Lenexa, Kansas, FDA District Office, which has inspection responsibilities for the Abbott Laboratories' manufacturing site in McPherson, Kansas.

Sincerely,

ABBOTT LABORATORIES

Amy Hartman

for

Jonathan Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
Fax: (847) 938-7867

ABBOTT

Hospital Products Division
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Abbott Park, Illinois 60064-6157

ORIG AMENDMENT

N/A M1

July 1, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler, Director
Glenn Smith, Chemistry Team Leader
Ted Palat, Project Manager

Re: ANDA 76-019 – Deferoxamine Mesylate for Injection, USP

Dear Sirs,

This correspondence is in reference to the July 16, 2002 Major Deficiency Letter which stated:

> ***"Review of Adverse Reaction Reports submitted to the Agency has indicated the potential for inflammatory reaction resulting from the use of Deferoxamine. These adverse reactions do not appear to be related to endotoxins and instead may be due to the presence of other agents in the drug substance which can elicit an inflammatory response. Please develop a method for screening your drug substance to prevent this type of adverse reaction and revise your drug substance specifications accordingly."***

Since receipt of the July 16, 2002 letter, Abbott Laboratories has conducted a very thorough investigation on the potential presence of 'other agents' in the [redacted] used to manufacture the Abbott drug product. A comprehensive summary of Abbott's investigation, including a proposed test, procedure and sensitivity to resolve the outstanding deficiency, is included in the attached report.

On March 17, 2003, the Agency sent Abbott a letter stating that a protocol with a proposed method could be submitted for review to the Office of Generic Drugs prior to the initiation of any studies or tests. Abbott hereby requests the Agency to review our proposal and provide their comments and/or recommendations. As we are ready to initiate these validation studies imminently, we would greatly appreciate immediate attention to this review and comments

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provided in the most expeditious manner. This would allow for a rapid resolution of this last outstanding issue, and subsequent approval of the subject abbreviated new drug application.

Abbott also acknowledges receipt of the May 2, 2003 correspondence. This letter reclassified the Major Deficiency to a Minor, and included the following:

> ***"Please note that we await your response to our Deficiency Letter dated July 16, 2002 requesting the development of a method for screening your drug substance to prevent inflammatory reactions not related to endotoxins. Please indicate that the response is a Minor Amendment."***

If you require any clarification or further information regarding this request, please feel free to contact me.

Very sincerely,

ABBOTT LABORATORIES

JDohnalek.

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
FAX: (847) 938-7867

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ORIG AMENDMENT

N/AC

October 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler, Director
Ted Palat, Project Manager

Re: ANDA 76-019 – Deferoxamine Mesylate for Injection, USP

Amendment – Expiration Dating Period, 500 mg & 2 g vials

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application.

In the original ANDA (October 31, 2000, page 446), we requested a 24-month expiration dating period for the 500 mg vial product, based upon satisfactory 3-month accelerated and long-term stability data on three exhibit sublots. ANDA Batch PD0-045 was sublotted to qualify three

On November 7, 2001, a major amendment was submitted to respond to two Agency action letters. At this time Abbott also added a new strength (2 gram vial), and provided satisfactory 9-month stability data on a new exhibit batch. A 24-month expiration dating period for the 2 gram vial was subsequently requested in the January 30, 2002 amendment (page 35).

On December 20, 2002, another amendment was submitted to provide for the addition of a new for the 2 gram vial product presentation. Satisfactory 3-month accelerated and long-term stability data on an additional exhibit batch was included. Expiration dating of 24 months was again proposed (December 20, 2002 amendment, page 115).

To support extension of the product dating periods to 30 months, additional data on the five ANDA exhibit lots (Product Lot Nos. PD0-045 , is provided as **Exhibit I**. Please note the 500 mg lot PD0-045 , did not meet the USP criteria for Constituted Solution in the 24-hour Reconstituted Stability Study at the 36-month interval. This lot, however, passed the specification at a 31-month test point.

Last year in anticipation of approval, Abbott manufactured and placed on stability additional drug product lots intended for commercial distribution. A kinetic/statistical analysis of potency, related substances and pH data on five (three exhibit and two commercial) 500 mg vial lots and five (two exhibit and three commercial) 2 g vial lots was prepared and is provided as **Exhibit II**.

Based upon all available data, **Abbott hereby requests approval of a 30-month expiration dating period for both products (500 mg and 2 g vials)**.

Section XVII – Stability of Finished Dosage Form has been updated to include the 30-month test station. The changes were limited to Section 1.B.i.1. (Initial Stability Study), Section 1.B.ii. (On-going stability Study) and Section 2. (Post-Approval Stability Commitment). A copy of the entire Section XVII is provided as **Exhibit III**. To facilitate review, the changes are identified using bold italic print. Abbott hereby commits that the 2 g Exhibit Lot PD2-189 [redacted], in addition to all commercial lots place on stability, will be tested through 30-months as noted in the revised protocol.

Abbott also acknowledges that our amendment addressing the Agency's major deficiency letter dated July 16, 2002 (re-classified as 'minor' on May 2, 2003) is still outstanding. Our developmental studies for a method to screen the drug substance to prevent inflammatory reactions will soon conclude. At that time, the minor amendment will be immediately submitted to fully respond to this last remaining issue.

In accordance with 21 CFR 314.94, Abbott Laboratories hereby certifies that we have submitted a complete copy of this Supplement (designated as the "field copy") to the Lenexa, Kansas, FDA District Office, which has inspection responsibilities for the Abbott Laboratories' McPherson, KS facility, where the drug product is manufactured.

If you require any clarification or further information regarding this amendment, please feel free to contact me.

Very sincerely,

ABBOTT LABORATORIES

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
FAX: (847) 938-7867

ABBOTT

AC

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ORIG AMENDMENT
N/AC

January 7, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler, Director
Ted Palat, Project Manager

Re: ANDA 76-019 – Deferoxamine Mesylate for Injection, USP

Minor Amendment – July 16, 2002 Deficiency Letter

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application to address the Agency's major deficiency letter dated July 16, 2002 (re-classified as 'minor' on May 2, 2003). This amendment is submitted to fully respond to the last remaining Agency review issue.

The Agency's July 16, 2002 comment was:

> ***"Review of Adverse Reaction Reports submitted to the Agency has indicated the potential for inflammatory reaction resulting from the use of Deferoxamine. These adverse reactions do not appear to be related to endotoxins and instead may be due to the presence of other agents in the drug substance which can elicit an inflammatory response. Please develop a method for screening your drug substance to prevent this type of adverse reaction and revise your drug substance specifications accordingly."***

As requested, we have developed a method to screen the drug substance to prevent the occurrence of a possible inflammatory reaction resulting from the use of our proposed drug product.

In our July 1, 2003 Amendment, Abbott proposed to validate and incorporate an *in vitro* [redacted] test into the specification of deferoxamine mesylate drug substance to screen for agents that elicit an inflammatory response. We anticipated validating a test at a sensitivity consistent with the level known to elicit human response to [redacted]. An [redacted] of "Not Detected by Test" (i.e., limit of detection) was proposed. The

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Page(s) of trade secret and /or confidential commercial information

The new drug substance [redacted] assay method described in **Exhibit II** will be provided in the first annual report.

ANDA Section IX - Description of the Manufacturing Facility, has been updated to include the following information:

> The drug substance [redacted] assay method will be performed in Abbott's North Chicago facility. The full address and Central File Number for this facility is:
>
> Abbott Laboratories
> 1401 N. Sheridan Road
> North Chicago, IL 60064
> CFN 1411365

Provided as **Exhibit III** is a cGMP certification letter issued by Abbott Laboratories, North Chicago, Illinois facility.

In accordance with 21 CFR 314.94, Abbott Laboratories hereby certifies that we have submitted a complete copy of this amendment (designated as the "field copy") to the Lenexa, Kansas, FDA District Office, which has inspection responsibilities for the Abbott Laboratories' McPherson, KS facility, where the drug product is manufactured.

We trust that this minor amendment completely addresses all of the Agency's concerns regarding this last outstanding issue, and will allow subsequent approval of the subject abbreviated new drug application. If you require any clarification or further information, please feel free to contact me.

Very sincerely,

ABBOTT LABORATORIES

JPDohnalek.

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
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ORIG AMENDMENT
N/A C

February 5, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler, Director
Ted Palat, Project Manager

Re: ANDA 76-019 – Deferoxamine Mesylate for Injection, USP

Amendment – Expiration Dating Period, 500 mg/vial and 2 g/vial

Reference is made to ANDA 76-019 and a teleconference between the Office of Generic Drugs (Glen J. Smith and Ted Palat) and Abbott Laboratories (Lisa K. Zboril and Jonathan Dohnalek) on Thursday, February 5, 2004. The Agency requested that Abbott submit a confirmatory request for a tentative expiration date assignment of 30-months for both the 500 mg/vial and 2 g/vial drug product presentations.

Abbott Laboratories hereby amend the above-referenced abbreviated new drug application as requested. Abbott hereby requests approval of a ***tentative 30-month*** dating period for both the 500 mg/vial and 2 gram/vial product presentations. We acknowledge that the tentative expiration date must be confirmed through the completion of real time testing through the 30 month interval on three post-approval commercial lots of each product presentation.

In accordance with 21 CFR 314.94, Abbott Laboratories hereby certifies that we have submitted a complete copy of this amendment (designated as the "field copy") to the Lenexa, Kansas, FDA District Office, which has inspection responsibilities for the Abbott Laboratories' McPherson, KS facility, where the drug product is manufactured.

We trust that this amendment completely addresses the Agency's concerns, and will allow subsequent approval of the subject abbreviated new drug application. If you require any clarification or further information, please feel free to contact me.

Sincerely,

ABBOTT LABORATORIES

JBDohnalek.

Jonathan P. Dohnalek
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Hospital Products Division
Phone: (847) 937-3413

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