

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-019

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #1
May 18, 2001

- A. 1. ANDA: 76-019
- APPLICANT: Abbott Laboratories, Inc.
200 Abbott Park Road
Abbott Park, IL 60064
2. PRODUCT NAME: Deferoxamine Mesylate for Injection, USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg/10 mL vial, lyophilized, for intramuscular, subcutaneous and intravenous injection, single use vials
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Iron-chelating agent
- B. 1. DATE OF INITIAL SUBMISSION: October 31, 2000
Subject of this Review (Received November 1, 2000)
2. DATE OF AMENDMENT: None
3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: May 10, 2001
- C. REMARKS: The subject drug product is to be produced on the
- D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the _____ process are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to the Applicant".

Lynne A. Ensor 5/18/01
Lynne A. Ensor, Ph. D.

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by L. Ensor, HFD 600 v:microrev\76019.doc
Initialed by A. High

CSW
6/7/01

E. REVIEW NOTES:

1. General Drug and Processing Descriptions. Each mL of the reconstituted drug contains 100 mg of deferoxamine mesylate and WFI. The drug product should be stored at 25°C or less. The product is to be reconstituted with sterile WFI (5 mL) and used immediately after reconstitution. When reconstituted under validated aseptic conditions, the product may be stored at room temperature for a maximum of 24 hours before use. The initial (maximum) dose is 1000 mg.



sterility testing and contained NMT (_____) p. 280, v.1.2).

The maximum production batch size is _____ and blank batch records are provided (p. 131 on, v. 1.1).

Acceptable

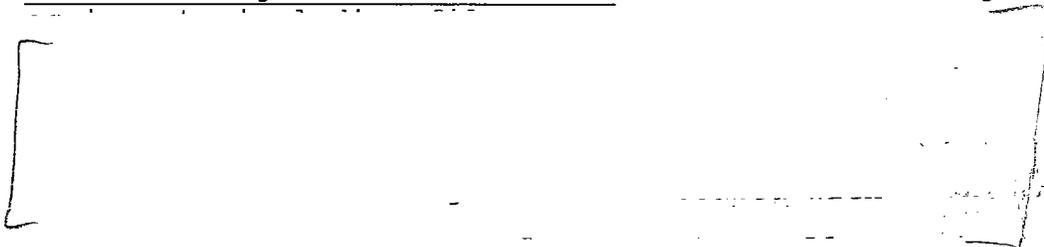
2. Facility and Environmental Control Descriptions. The drug product is manufactured and stability tested at:

Abbott Laboratories
1766 N. Centennial Drive
McPherson, KS 67460

This facility is cGMP certified (p. 82, v. 1.1). Floor plans, with descriptions of the room classifications, personnel/component flow, and equipment locations indicated on them, are provided (v.1.1, p.110-116).

Acceptable

3. Manufacturing and Product Flow. All manufacturing



Redacted 15

Page(s) of trade

secret and /or

confidential

commercial

information

Product Quality Microbiology Review

Review for HFD-640

June 3, 2002

ANDA: 76-019

Drug Product Name

Non-proprietary: Deferoxamine Mesylate for Injection, USP

Drug Product Classification: Iron-chelating agent

Review Number: 2

Subject of this Review

Submission Date: November 7, 2001

Receipt Date: November 8, 2001

Consult Date: NA

Date Assigned for Review: May 16, 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): October 31, 2000

Date(s) of Previous Micro Review(s): May 18, 2001

Applicant/Sponsor

Name: Abbott Laboratories, Inc.

Address: 200 Abbott Park Road
Abbott Park, IL 60064

Representative: Jean Kirkeleit Davis

Telephone: (847) 935-9873

Name of Reviewer: Lynne Ensor

Conclusion: Recommended

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUPPLEMENT:** NA
- 2. **SUPPLEMENT PROVIDES FOR:** NA
- 3. **MANUFACTURING SITE:** Abbott
- 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 500 mg/10 mL vial, lyophilized, for intramuscular, subcutaneous and intravenous injection, single use vials
- 5. **METHOD(S) OF STERILIZATION:** _____
- 6. **PHARMACOLOGICAL CATEGORY:** Iron-chelating agent
- B. **SUPPORTING/RELATED DOCUMENTS:** none
- C. **REMARKS:** The subject amendment provides responses to the Agency's June 12, 2001 deficiency letter.
 The subject drug product is to be produced on the _____

filename: v:microrev\76190a1.doc

**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

I. Recommendations

- A. Recommendation on Approvability - Recommended
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA

II. Summary of Microbiology Assesments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - _____
- B. Brief Description of Microbiology Deficiencies - none
- C. Assessment of Risk Due to Microbiology Deficiencies – none identified

III. Administrative

A. Reviewer's Signature *L. Ensor* 6/14/02
Lynne A. Ensor, Ph.D.

B. Endorsement Block
L. Ensor
F. Holcombe *F. Holcombe* 6/14/02

C. CC Block
cc:
Original ANDA 76-019
HFD- 600 v:\microrev\76019a1.doc

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 3

Page(s) of trade

secret and /or

confidential

commercial

information

Product Quality Microbiology Review

Review for HFD-640

April 16, 2003

ANDA: 76-019

Drug Product Name

Proprietary: n/a
Non-proprietary: Deferoxamine Mesylate for Injection, USP
Drug Product Classification: n/a

Review Number: 3

Subject of this Review

Submission Date: December 20, 2002 (gratuitous amendment)
Receipt Date: December 23, 2002
Consult Date: n/a
Date Assigned for Review: April 11, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): October 31, 2000 (original) &
November 7, 2001 (amendment
addressing microbiology deficiencies
from the original submission)
Date(s) of Previous Micro Review(s): May 18, 2001 & June 3, 2002

Applicant/Sponsor

Name: Abbott Laboratories
Address: 200 Abbott Park Road D-389 J45/2
Abbott Park, IL 60064
Representative: Jonathan Dohnalek
Telephone: 847-937-3413

Name of Reviewer: Lynne Ensor

Conclusion: Recommended

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUPPLEMENT:** n/a
 2. **AMENDMENT PROVIDES FOR:** _____
 3. **MANUFACTURING SITE:** McPherson, KS
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile powder in vials, for injection, 500 mg/vial and 2 g/vial
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** antibiotic

B. SUPPORTING/RELATED DOCUMENTS:
 ANDAs 62-911/SCS-012 & 62-912/SCS-011 –
 The microbiology reviewer ‘recommended’ the use of _____ on the basis of product sterility assurance in the 9/24/02 microbiology review prepared by L. Ensor.

C. REMARKS: The subject gratuitous amendment provides for an alternate _____ Prior to the submission of the subject amendment, the original application was ‘recommended’ for approval on the basis of sterility assurance of the subject drug product in the 9/24/02 microbiology review (prepared by L. Ensor). This review is the first time that the information contained within the subject amendment has been reviewed for sterility assurance.

The proposed alternate _____ was ‘recommended’ in the 9/24/02 microbiology review for ANDAs 62-911/SCS-012 and 62-912/SCS-011 (prepared by L. Ensor) to be used in the _____ manufacture of a similar sterile generic drug product. The cycle proposed in the subject amendment used to _____ is the same as the cycle proposed in ANDAs 62-911/SCS-012 and 62-912/SCS-011.

filename: v:\microrev\76019a2.doc

Executive Summary

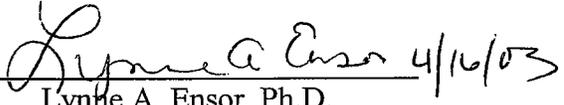
I. Recommendations

- A. **Recommendation on Approvability** - recommended
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – n/a

II. Summary of Microbiology Assesments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug solution is _____
_____ (proposed in the subject amendment) or the _____ proposed in the original submission
- B. **Brief Description of Microbiology Deficiencies** – none identified
- C. **Assessment of Risk Due to Microbiology Deficiencies** - minimal

III. Administrative

- A. **Reviewer's Signature**  4/16/03
Lynne A. Ensor, Ph.D.
- B. **Endorsement Block**
L. Ensor
N. Sweeney  4/17/03
- C. **CC Block**
cc:
Original ANDA
Division File
Field Copy

Redacted 2

Page(s) of trade

secret and /or

confidential

commercial

information

Product Quality Microbiology Review
Review for HFD-640

July 22, 2003

ANDA: 76-019

Drug Product Name

Proprietary: n/a
Non-proprietary: Deferoxamine Mesylate for Injection, USP
Drug Product Classification: n/a

Review Number: 4

Subject of this Review

Submission Date: July 1, 2003 (gratuitous amendment)
Receipt Date: July 2, 20003
Consult Date: n/a
Date Assigned for Review: July 18, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): October 31, 2000 (original)
November 7, 2001 (amendment
addressing microbiology deficiencies
from the original submission)
December 20, 2002 (gratuitous amendment)

Date(s) of Previous Micro Review(s): May 18, 2001, June 3, 2002 &
April 16, 2003

Applicant/Sponsor

Name: Abbott Laboratories
Address: 200 Abbott Park Road D-389 J45/2
Abbott Park, IL 60064
Representative: Jonathan Dohnalek
Telephone: 847-937-3413

Name of Reviewer: Lynne Ensor

Conclusion: The protocol proposed is **adequate** to be used for the
development of further studies regarding the proposed test method.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUPPLEMENT:** n/a
2. **AMENDMENT PROVIDES FOR:** the proposal of an in-process test for the drug substance to detect contaminants that may potentially cause an inflammatory response in patients using the drug product.
3. **MANUFACTURING SITE:** McPherson, KS
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile powder in vials, for injection, 500 mg/vial and 2 g/vial
5. **METHOD(S) OF STERILIZATION:**
6. **PHARMACOLOGICAL CATEGORY:** antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** none
- C. **REMARKS:** The subject gratuitous amendment proposes an in-process test method to be used for the drug substance. A similar in-process test method and specification are currently approved for the innovator drug product. The innovator's in-process test method and specification was developed as a result of inflammatory responses reported in patients which were later determined to be a result of contaminants present in the drug substance.

filename: v:\microrev\76019a3.doc

**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

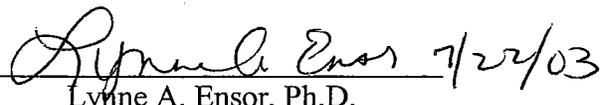
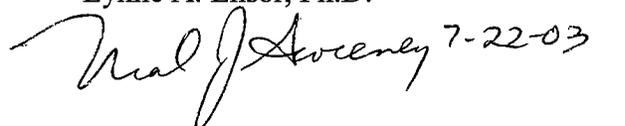
I. Recommendations

- A. **Recommendation on Approvability** - The protocol proposed is adequate to be used for the development of further studies regarding the proposed test method.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – n/a

II. Summary of Microbiology Assesments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug solution is _____
- B. **Brief Description of Microbiology Deficiencies** – none identified
- C. **Assessment of Risk Due to Microbiology Deficiencies** – n/a

III. Administrative

- A. **Reviewer's Signature**  7/22/03
Lynne A. Ensor, Ph.D.
- B. **Endorsement Block**  7-22-03
L. Ensor
N. Sweeney
- C. **CC Block**
cc:
Original ANDA
Division File
Field Copy

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

**Product Quality Microbiology Review
Review for HFD-640**

January 22, 2004

ANDA: 76-019

Drug Product Name

Proprietary: n/a

Non-proprietary: Deferoxamine Mesylate for Injection, USP

Drug Product Classification: n/a

Review Number: 5

Subject of this Review

Submission Date: January 7, 2004 (amendment)

Receipt Date: January 8, 2004

Consult Date: n/a

Date Assigned for Review: January 21, 2004

Submission History (for amendments only)

Date(s) of Previous Submission(s): October 31, 2000 (original)

November 7, 2001 (amendment

addressing microbiology deficiencies
from the original submission)

December 20, 2002 (gratuitous amendment)

July 1, 2003 (gratuitous amendment)

Date(s) of Previous Micro Review(s): May 18, 2001, June 3, 2002,
April 16, 2003 & July 22, 2003

Applicant/Sponsor

Name: Abbott Laboratories

Address: 200 Abbott Park Road D-389 J45/2
Abbott Park, IL 60064

Representative: Jonathan Dohnalek

Telephone: 847-937-3413

Name of Reviewer: Lynne Ensor

Conclusion: The test method proposed is **adequate** to screen the drug substance prior to use in the drug product

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUPPLEMENT:** n/a
2. **AMENDMENT PROVIDES FOR:** an in-process test for the drug substance to detect contaminants that may potentially cause an inflammatory response in patients using the drug product.
3. **MANUFACTURING SITE:** McPherson, KS
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile powder in vials, for injection, 500 mg/vial and 2 g/vial
5. **METHOD(S) OF STERILIZATION:** _____
6. **PHARMACOLOGICAL CATEGORY:** antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** none
- C. **REMARKS:** The subject amendment provides for an in-process test method to be used for the drug substance. A similar in-process test method and specification are currently approved for the innovator drug product. The innovator's in-process test method and specification was developed as a result of inflammatory responses reported in patients which were later determined to be a result of contaminants present in the drug substance.

filename: v:\microrev\76019a4.doc

**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

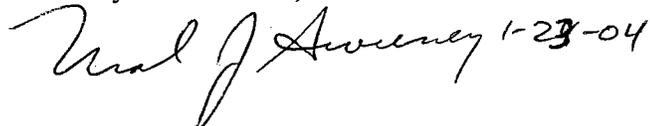
I. Recommendations

- A. **Recommendation on Approvability** – the test method is **adequate** for its intended purpose
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – n/a

II. Summary of Microbiology Assesments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug solution is _____
- B. **Brief Description of Microbiology Deficiencies** – none identified
- C. **Assessment of Risk Due to Microbiology Deficiencies** – n/a

III. Administrative

- A. **Reviewer's Signature**  1/22/04
Lynne A. Ensor, Ph.D.
- B. **Endorsement Block**  1-23-04
L. Ensor
N. Sweeney
- C. **CC Block**
cc:
Original ANDA
Division File
Field Copy

Redacted 2

Page(s) of trade

secret and /or

confidential

commercial

information