CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76018

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #1

June 7, 2001

A. 1. **ANDA:** 76-018

APPLICANT: Bedford Laboratories
300 Northfield Rd.
Bedford, Ohio 44146

2. PRODUCT NAME: Amiodarone HCL Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Amiodarone HCl Injection is an aqueous solution that is packaged into 5 mL vials (3 mL fill) at a concentration of 50 mg/mL that must be diluted prior to intravenous administration.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Anti-arrhythmic drug

B. 1. DATE OF INITIAL SUBMISSION: October 27, 2000
Subject of this Review (Received November 1, 2000)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS:
DMF drug substance
DMF vials
DMF stoppers

4. ASSIGNED FOR REVIEW: May 31, 2001

C. REMARKS: Amiodarone HCl Injection, 50 mg/mL is manufactured for Bedford Laboratories by Ben Venue Laboratories Inc. in Bedford, Ohio. The subject drug product is sterilized by

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 "Microbiology Comments to be Provided to the Applicant".

/S/ 6/27/01

Marla Stevens-Riley, Ph. D.

6/27/01

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by M. Stevens-Riley, HFD 600 v:microrev\76-018
Initialed by M. Fanning/A. High

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Microbiology Review #1

Microbiology Comments to be Provided to the Applicant

ANDA: 76-018 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Amiodarone HCl Injection, 50 mg/mL

A. Microbiology Deficiencies:

1. With regard to in-process sterilization:

   a. Please provide D values for all of the BIs used for sterilization validation of the stoppers and equipment, and please indicate whether or not you confirmed the concentration of all BIs.

   b. Please indicate the validation parameters for the equipment sterilization.

   c. There are inconsistencies with the narrative description of equipment sterilization validation in Vol. 1.3, p. 121 and the "Documentation Format for Annual Equipment Sterilization Cycle Verification Procedure" in Vol. 1.3, pp. 228 and 259. The biological indicator information is not complete, the biological indicators are not the same, Challenge study #V15396S is not present, and data for 3 consecutive minimum and maximum heat penetration/BI runs are not present. Please explain the inconsistencies and provide 3 consecutive successful runs for validation of the equipment sterilization (as stated in the your validation criteria in Vol. 1.3, p. 121).

2. With regard to validation:

   a. Please provide run data for the last 3 most recent fills that include vial and closure sizes representative of the finished drug product for each filling line 111 and 112.

   b. Please indicate how the duration of the relates to production.

3. Please explain why the assay for filter validation was only minutes in length.

4. The endotoxin limit should be recalculated based upon the statement in Vol. 1.1, p. 37 in the "Dosage and Administration" section of the package insert, "The initial infusion rate should not exceed mg/minute." Your current limit does not include this maximum possible initial dose.

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

Please clearly identify your amendment to this facsimile as □RESPONSE TO MICROBIOLOGY DEFICIENCIES□. The □RESPONSE TO MICROBIOLOGY DEFICIENCIES□ should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review

January 9, 2002

ANDA: 76-018

Name of Drug: Amiodarone HCl Injection

Review Number: 2

Submission Date: September 25, 2001

Applicant: Bedford Laboratories

Name of Reviewer: Marla Stevens-Riley

Product Quality Microbiology Data Sheet

A. 1. **ANDA:** 76-018

2. **REVIEW NUMBER:** 2

3. **REVIEW DATE:** January 9, 2002

4. **TYPE OF SUPPLEMENT:** N/A

5. **SUPPLEMENT PROVIDES FOR: N/A**

6. **APPLICANT/SPONSOR:**

Name: Bedford Laboratories
Representative: Molly L. Rapp
Telephone: 440-201-3576

7. **MANUFACTURING SITE:** Bedford, Ohio, USA

8. **DRUG PRODUCT NAME:**
Proprietary: N/A
Non-proprietary: Amiodarone HCl Injection
Drug Priority Classification: N/A

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Amiodarone HCl Injection is an aqueous solution that is packaged into 5 mL vials (3 mL fill) at a concentration of 50 mg/mL that must be diluted prior to intravenous administration. Reviewed prepared for HFD-640.

10. **METHOD(S) OF STERILIZATION:**

11. **PHARMACOLOGICAL CATEGORY:** Anti-arrhythmic

B. 1. **DOCUMENT/LETTER DATE:** October 27, 2000
2. **RECEIPT DATE:** N/A
3. **CONSULT DATE:** N/A
4. **DATE OF AMENDMENTS:** September 25, 2001
Subject of this review (September 27, 2001)

Telephone amendment, January 18, 2002
Subject of this review (January 22, 2002)

5. **ASSIGNED FOR REVIEW:** January 4, 2002
6. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** The subject amendment provides for the response to the Microbiology deficiencies dated July 3, 2001. The subject drug product is sterilized [redacted]

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology-
The subject drug product is sterilized

B. Brief Description of Microbiology Deficiencies-None

C. Assessment of Risk Due to Microbiology Deficiencies-None

III. Administrative

A. Reviewer's Signature /S/ 1/25/02

B. **Endorsement Block** /S/ 1/25/02
Marla Stevens-Riley/ 1/25/02
L. Ensor/
B. McNeal/

C. CC Block
cc:
Original ANDA 76-018
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micro Review #2