CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-025

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

03 APR 2007

NDA: 22-025 AZ, BL and BI

Drug Product Name
Proprietary: Totect™
Non-proprietary: Dexrazoxane
Drug Product Priority Classification: 5S

Review Number: 3

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
22-NOV-2006	24-NOV-2006	09-JAN-2007	10-JAN-2007
24-JAN-2007	25-JAN-2007	N/A	N/A
21-MAR-2007	23-MAR-2007	N/A	N/A
26-MAR-2007	28-MAR-2007	N/A	28-MAR-2007

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
31-JAN-2006	1	12-JUL-2006
14-JUN-2006	1	12-JUL-2006
24-JUL-2006	2	29-AUG-2006

& memo dated 21-SEP-2006 for N-000 MP submitted on 07-SEP-2006

Applicant/Sponsor
Name: Alba BioPharm Advisors, Inc. (US Agent for TopoTarget (Copenhangen, Denmark)
Address: 12109 Betts Lane
Raleigh, NC 27614

Representative: William McCulloch, Ph.D.
Telephone: 919-848-6495
E-mail: bmcculloch@albaadvice.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Recommended for approval

APPEARS THIS WAY ON ORIGINAL

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** AZ amendment to NDA

2. **SUBMISSION PROVIDES FOR:** Response to chemistry and microbiology deficiencies and changes in the manufacturing facilities involved as discussed during the industry meeting on 02-OCT-2006

3. **MANUFACTURING SITE:**

Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146

b(4)

2) Hameln Pharmaceuticals GmbH
Langes Feld 13
31789 Hameln, Germany

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Sterile lyophilized powder (500 mg/vial) and solvent (50 mL/vial) in glass vials
   - Intravenous infusion
   - 10 mg/mL

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

b(4)

6. **PHARMACOLOGICAL CATEGORY:** Detoxifying agent for antineoplastic agents for the treatment of anthracycline extravasation during chemotherapy

B. **SUPPORTING/RELATED DOCUMENTS:**
   - Memo dated 21-SEP-2006 in preparation for the industry meeting discussion on 02-OCT-2006. Also, see meeting minutes in DFS.
   - Microbiology Reviews #1 and #2 of NDA 22-025 dated 12-JUL-2006 and 29-AUG-2006.
   - Microbiology Reviews #1 and #2 of ANDA 76-068 dated 17-DEC-2003 and 12-MAR-2004.
   - OGD Microbiology Reviews #17-24 of Type V DMF — dating from November 2005 to January 2007. There are also several NDMS reviews. All depyrogenation and sterilization processes including process simulations have been reviewed regarding — suites 11 and 13 (North Complex), 4147 and 4165 (Addition to North Complex) and 111, 112 and 1151 (South Complex). Any deficiencies have been addressed or are in the process of being addressed. The last DMF review of —

b(4)

b(4)

b(4)

———, was in late 2003/early 2004 (OGD Microbiology Reviews #12 and 12a1). b(4)

C. **REMARKS:** This is a paper submission in the CTD format. Modules 1-3 were provided for review.

This NDA originally received an "Approvable" recommendation due to many microbiology deficiencies identified for the manufacture of both the lyophilized powder and companion solvent. A major issue was also that fact that the facility ——— b(4)
product was not ready for inspection during the review of the NDA. Several communications followed and a meeting with the firm where the firm proposed to ——— Ben Venue Laboratories (Bedford, OH) for the manufacture ——— b(4)
. The Ben Venue site already manufactures the same drug product as approved in ANDA 76-068 (the brand name product is Pfizer's Zinecard®). ———

The applicant also proposes to have the ——— manufactured at the Hameln Pharmaceuticals GmbH site in Germany as proposed in the original NDA submission. b(4)

An information request was sent to the applicant on March 19, 2007 by the OND Project Manager to provide the following:

Solvent, Hameln Pharmaceuticals:

1. Provide a summary of the last requalification of the vial washer to demonstrate its efficacy in rinsing vials adequately.

2. Provide a summary of validation studies that demonstrate the efficacy of the washing process to remove bacterial endotoxins from the ——— stoppers b(4)

Lyophilized Powder:

1. Provide bacterial filter retention studies that support the manufacture of a ——— batch size. The studies provided (performed for ANDA 76-068) did not simulate the proposed batch size. b(4)

2. Provide a data summary of the method validation for the bacterial endotoxins test at the lower limit of ———

A BI amendment was submitted on March 26, 2007 and the applicant's responses have been incorporated in the relevant sections of the review. A desk copy was provided but the amendment was also submitted as an electronic document.

file name: N022025R3.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval based on product quality microbiology

B. Recommendations 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 applicant provides responses to the deficiencies identified in the "Approvable" letter.

[redacted] b(4)

This review evaluates the responses to the deficiencies as well as product quality microbiology aspects as related to the addition of the Ben Venue manufacturing site.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
James L. McVey

C. CC Block
N/A

11 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology-1

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/s/

Anastasia Lolas
4/5/2007 02:02:40 PM
MICROBIOLOGIST

James McVey
4/5/2007 02:14:19 PM
MICROBIOLOGIST

Product Quality Microbiology Review

29 AUG 2006

NDA: 22-025 BC

Drug Product Name
Proprietary: Totect™
Non-proprietary: Dexrazoxane
Drug Product Priority Classification: P

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
24-JUL-2006	25-JUL-2006	07-AUG-2006	07-AUG-2006

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
31-JAN-2006	1	12-JUL-2006
14-JUN-2006	1	12-JUL-2006

Applicant/Sponsor
Name: Alba BioPharm Advisors, Inc. (US Agent for TopoTarget, Copenhangen, Denmark)
Address: 12109 Betts Lane
Raleigh, NC 27614

Representative: William McCulloch, Ph.D.
Telephone: 919-848-6495
E-mail: bmcculloch@albaadvice.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Approvable pending the resolution of microbiology deficiencies identified in the first microbiology review

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** BC Amendment to Original NDA

2. **SUBMISSION PROVIDES FOR:** Response to certain deficiencies communicated to the applicant in Microbiology Information Requests dated 11-MAY-2006 and 22-JUN-2006 and Chemistry Information Request dated 09-JUN-2006

3. **MANUFACTURING SITE:**
Drug Substance:
Manufacturing site:

b(4)

Drug Product:

Hameln Pharmaceuticals GmbH
Langes Feld 13
31789 Hameln
Germany

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Sterile lyophilized product (500 mg/vial) and solvent (50 mL/vial) in glass vials
- Intravenous infusion
- 10 mg/mL

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

b(4)

6. **PHARMACOLOGICAL CATEGORY:** Detoxifying agents for antineoplastic agents for the treatment of anthracycline extravasation during chemotherapy

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** In this amendment, the applicant offered additional clarification on one question and two comments that had been communicated in an Information Request dated 11-MAY-2006. Even though a response was submitted on 14-JUN-2006, the applicant felt that additional clarification was necessary. In addition, the applicant provide a brief response to the 22-JUN-2006 Information Request.

These responses do not resolve the microbiology deficiencies identified in the first microbiology review and therefore, the recommendation for this NDA remains "Approvable" from the product quality microbiology perspective.

file name: N022025R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending the resolution of microbiology deficiencies identified in the first microbiology review

B. Recommendations 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 product consists of a glass vial with a lyophilized powder and a glass vial that contains the sodium lactate for injection (USP) solvent for reconstitution. The [redacted] b(4)

B. Brief Description of Microbiology Deficiencies - The [redacted] There are inconsistencies and inadequate data to support the [redacted] sterilization of the solvent. b(4)

C. Assessment of Risk Due to Microbiology Deficiencies - The risk to the patient is high because without adequate sterilization validation data, the sterility of the product is not assured.

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
James L. McVey

C. CC Block
N/A

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_____ Deliberative Process (b5)

Withheld Track Number: Microbiology- 2

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/s/

Anastasia Lolas
8/30/2006 11:14:56 AM
MICROBIOLOGIST

James McVey
9/1/2006 09:18:46 PM
MICROBIOLOGIST

Product Quality Microbiology Review

12 JUL 2006

NDA: 22-025
22-025 BZ

Drug Product Name
Proprietary: Totect™
Non-proprietary: Dexrazoxane
Drug Product Priority Classification:

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
31-JAN-2006	01-FEB-2006	01-MAR-2006	03-MAR-2006
14-JUN-2006	15-JUN-2006	N/A	26-JUN-2006

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Alba BioPharm Advisors, Inc. (US Agent for TopoTarget (Copenhangen, Denmark)
Address: 12109 Betts Lane
Raleigh, NC 27614

Representative: William McCulloch, Ph.D.
Telephone: 919-848-6495
E-mail: bmcculloch@albaadvice.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Approvable pending the resolution of microbiology deficiencies (see Section 3 of review)

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** New Drug Application

2. **SUBMISSION PROVIDES FOR:** New drug product

3. **MANUFACTURING SITE:**

[redacted] b(4)

Drug Product:

[redacted]

Hameln Pharmaceuticals GmbH
Langes Feld 13
31789 Hameln
Germany

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Sterile lyophilized product (500 mg/vial) and solvent (50 mL/vial) in glass vials
   - Intravenous infusion
   - 10 mg/mL

5. **METHOD(S) OF STERILIZATION:** [redacted] b(4)

6. **PHARMACOLOGICAL CATEGORY:** Detoxifying agents for antineoplastic agents for the treatment of anthracycline extravasation during chemotherapy

B. **SUPPORTING/RELATED DOCUMENTS:**
   - DMF [redacted] July 2005 update; the efficacy of the washing process to remove endotoxin from the [redacted] stoppers was reviewed and found inadequate. The DMF holder subsequently responded that they do not provide a certificate that the stoppers are free of endotoxin and ready-to-sterilize. It is the responsibility of the customer to ensure this (see Microbiology Reviews #1 and #2 dated 10-MAY-2006 and 22-JUN-2006). b(4)

C. **REMARKS:** The drug product has been designated as an orphan drug. It consists of a lyophilized powder and a solvent.

Chiron Corporation Ltd. markets Cardioxane®, dexrazoxane powder for infusion in Europe. [redacted] r is manufactured at [redacted] Therefore, [redacted] b(4)

The [redacted] is manufactured at [redacted] and is used for the dexrazoxane product (Zinecard®) marketed in the US by Pfizer, Inc. This product was approved by the Agency in NDA 20-212 but the applicant does not have a right of reference to it. b(4)

The applicant was contacted on May 11, 2006 to provide additional information. A BZ amendment was submitted on June 14, 2006. A second information request was sent on June 22, 2006 regarding the processing of the [redacted] stoppers (after the review of DMF [redacted] and communication with the DMF holder). b(4)

The manufacturing site in Belgium is not ready for inspection until January 2007 (see BC amendment dated 31-MAR-2006). The Germany site has an acceptable status based on file review.

APPEARS THIS WAY ON ORIGINAL

file name: N022025R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending the resolution of microbiology deficiencies (see Section 3 of review)

B. Recommendations 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 product consists of a glass vial with a lyophilized powder and a glass vial that contains the sodium lactate for injection (USP) solvent for reconstitution. The lyophilized product is ——— filled while the solvent is ——— filled followed by ——— sterilization. b(4)

B. Brief Description of Microbiology Deficiencies – The product-specific filter bacterial retention study for the lyophilized product is not complete yet. There are inconsistencies and inadequate data to support the terminal sterilization of the solvent.

C. Assessment of Risk Due to Microbiology Deficiencies – The risk to the patient is high because without adequate sterilization validation data, the sterility of the product is not assured.

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
Bryan S. Riley, Ph.D.

C. CC Block
N/A

24 Page(s) Withheld

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Withheld Track Number: Microbiology- 3

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/s/

Anastasia Lolas
7/13/2006 09:06:09 AM
MICROBIOLOGIST

Bryan Riley
7/13/2006 09:46:56 AM
MICROBIOLOGIST