CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

18 October 2012

NDA: 022-453/N000

Drug Product Name
Proprietary: To be determined
Non-proprietary: Topotecan Hydrochloride Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
22 June 2012	25 June 2012	05 July 2012	13 July 2012
12 October 2012 (SD 17)	12 October 2012	NA	NA

Submission History (for amendments only) –

Submit Date(s)	Microbiology Review #	Review Date(s)
17 December 2008	1	09 July 2009
08 May 2009	1	09 July 2009
21 May 2009	1	09 July 2009
16 June 2009	1	09 July 2009

Applicant/Sponsor
Name: Teva Parenteral Medicines, Inc.
Address: 19 Hughes
Irvine Ca 92618
Representative: Susan O'Brien
Telephone: (949) 455-4724

Name of Reviewer: Denise A. Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Class 2 Resubmission

2. SUBMISSION PROVIDES FOR: CMC changes in response to inspectional deficiencies at the manufacturing site.

3. MANUFACTURING SITE:

Teva Parenteral Medicines, Inc
19 Hughes
Irvine CA 92618-1902
Drug Establishment Registration No. 000703 2027158

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Dosage Form: Sterile liquid for Injection 4 mL fill in a (b) (4) vial
- Route of Administration: Intravenous infusion
- Strength/Potency: 1 mg Base/mL

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: chemotherapy

B. SUPPORTING/RELATED DOCUMENTS:

1) Quality Microbiology Review #1 N022453N000R1.doc dated 09 July 2009 recommendation was to approve the application based on the quality microbiology information provided.

2) OGD review (b) (4) of DMF (b) (4) for submission of 22 November 2011 (b) (4)

C. REMARKS:

1) Application is in e-CTD format.
2) An information request was sent on 01 October 2012 for which a response was received on 12 October 2012 as supporting document 17.

filename: N022453N000R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend to approve from a quality microbiology standpoint.

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product is sterile (b) (4)

B. Brief Description of Microbiology Deficiencies – None identified.

C. Assessment of Risk Due to Microbiology Deficiencies - NA

III. Administrative

A. Reviewer's Signature _____

Denise A. Miller
Microbiologist, OPS/NDMS

B. Endorsement Block _____

Stephen E. Langille, Ph.D.
Senior Microbiologist, OPS/NDMS

C. CC Block

N/A

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/s/

DENISE A MILLER
10/23/2012

STEPHEN E LANGILLE
10/24/2012

Product Quality Microbiology Review

09 July 2009

NDA: **22-453/N000**

Drug Product Name
Proprietary: None
Non-proprietary: Topotecan Hydrochloride Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
17-DEC-2008	18-DEC-2008	06-JAN-2009	13-JAN-2009
08-MAY-2009 (BL)	08-MAY-2009	NA	NA
21-MAY-2009 (BI)	21-MAY-2009	NA	NA
16-JUN-2009 (BZ)	16-JUN-2009	NA	NA

Submission History (for amendments only) - N/A

Applicant/Sponsor
Name: Teva Parenteral Medicines, Inc.
Address: 19 Hughes
Irvine, CA 92618
Representative: Susan O'Brien
Telephone: (949) 455-4724

Name of Reviewer: Denise Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original application

2. SUBMISSION PROVIDES FOR: New drug

3. MANUFACTURING SITE:

Teva Parenteral Medicines, Inc.
19 Hughes
Irvine, CA 92618-1902
Drug Establishment Registration No. 000703 2027158

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Liquid, 4 mL fill in a (b) (4) vial
- Intravenous Infusion
- 1 mg Base/mL

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: chemotherapy

B. SUPPORTING/RELATED DOCUMENTS: NA

C. REMARKS:

- This submission was in e-CTD format.
- The filing review identified that there was no post (b) (4) storage conditions listed on the label. The label was updated with a BL amendment dated 08-MAY-2009.
- The validation report for the (b) (4) was submitted in a BI amendment dated 21-MAY-2009 in response to an Information Request.
- The sponsor was contacted via telephone on 10-JUN-2009 for clarifications on the (b) (4) validation report. In response, a BZ amendment was submitted on 16-JUN-2009 with an updated report.

filename: N022453N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend to approve from a quality microbiology standpoint

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 - Sterile [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies - none

C. Assessment of Risk Due to Microbiology Deficiencies - NA

III. Administrative

A. Reviewer's Signature _____
Denise Miller, Microbiologist

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

C. CC Block
N/A

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/s/

Denise Miller
7/13/2009 10:28:12 AM
MICROBIOLOGIST

Bryan Riley
7/13/2009 10:43:21 AM
MICROBIOLOGIST
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 022-453 **Applicant: TEVA Parenteral** **Letter Date:** 17-DEC-2008

Drug Name: Topotecan Hydrocholoride Injection **NDA Type: 505(b)(2)** **Stamp Date:** 18-DEC-2008

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	√		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	√		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		√	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	√		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		
7	Has the applicant submitted the results of analytical method verification studies?	√		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	NA		
9	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:
1) submission is e-CTD format.
2) Label does not provide a time limit for use after dilution into IV fluids. The sponsor should update the label with time limits which should be supported by microbial stability studies. In lieu of microbial studies, the time limit should be restricted to Not More Than (NMT) 4 hours at room temperature or NMT 12 hours refrigerated.

Reviewing Microbiologist Date

Microbiology Secondary Reviewer/Team Leader Date

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/s/

Denise Miller
1/26/2009 09:11:42 AM
MICROBIOLOGIST

Bryan Riley
1/26/2009 09:25:22 AM
MICROBIOLOGIST
I concur.