

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**0200199Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

10-18-2010

**NDA: 200-199/N-000**

**Drug Product Name**

**Proprietary:** N/A

**Non-proprietary:** Topotecan Injection

**Review Number: 1**

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
27-JAN-2010	27-JAN-2010	03-MAR-2010	04-MAR-2010
25-MAR-2010	25-MAR-2010	N/A	N/A
20-SEP-2010	20-SEP-2010	N/A	N/A
05-OCT-2010	05-OCT-2010	N/A	N/A

**Applicant/Sponsor**

**Name:** Sandoz Inc.

**Address:** 506 Carnegie Center  
Princeton, NH 08540

**Representative:** Bernadette Attinger  
Director, Regulatory Affairs

**Telephone:** 267-291-1225

**Name of Reviewer:** Steven E. Fong, Ph.D.

**Conclusion:** CMC-Microbiology recommends APPROVE.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
  2. **SUBMISSION PROVIDES FOR:** New drug product.
  3. **MANUFACTURING SITES:**

**Drug Product Manufacturing Site:**

Ebewe Pharma Ges.m.b.H.  
Nfg.KG  
Mondseestrasse 11  
A-4866 Unterach, Austria  
Est. Reg. #3002829723

**Drug Substance Manufacturing Sites:**



4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 1 mg/mL sterile solution injection provided as a 1 mg/1 mL solution in 2 mL vials, and 3 mg/3 mL and 4 mg/4 mL solutions in 5 mL vials. The product is intended for intravenous infusion after dilution in saline or dextrose.
5. **METHOD(S) OF STERILIZATION:**  (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Cancer therapeutic.

B. **SUPPORTING/RELATED DOCUMENTS:**

- DMF  (b) (4) describing manufacture and  (b) (4) at  (b) (4), and a LOA from  (b) (4) dated 05-MAY-2009 authorizing Agency review of the DMF.
- 05-AUG-2010 microbiology quality review of  (b) (4) procedures described in DMF  (b) (4)

**C. REMARKS:**

- The application was submitted electronically in CTD format.
- The application is a Section 505(b)(2) submission. The reference listed drug that is the basis of the application is Hycamtin® (Topotecan Hydrochloride for Injection). Hycamtin® was approved under NDA 20-671 and is marketed by GlaxoSmithKline.
- In the original application Sandoz proposed drug product manufacture at (b) (4) as well as Ebewe Pharma. (b) (4) was withdrawn as a manufacturing site in an amendment received 25-MAR-2010.
- Manufacture of drug substance sourced from (b) (4) is described in DMF (b) (4). A LOA dated 06-MAY-2009 permitting Agency review of the file was provided with the application.
- Manufacture of drug substance sourced from (b) (4) is described in DMF (b) (4). A LOA dated 06-MAY-2009 permitting Agency review of the file was provided with the application.
- On 14-SEP-2010 an IR was sent to the applicant requesting a response to the following:
  - (1) *The Preparation for Intravenous Administration section of the proposed label states that the ‘ (b) (4) Microbiological data should be provided in the NDA to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. The studies should include analyses conducted with product diluted to the maximum allowable limit in dextrose and saline.*

*Generally, "no growth" is interpreted as not more than a 0.5 log<sub>10</sub> increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers ( $\leq 100$  CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should*

*recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours at refrigerated temperature.*

(2)



These items were discussed in a teleconference held with the applicant on 16-SEP-2010. An amendment response was received 20-SEP-2010 (supporting document 8).

- On 04-OCT-2010 a second IR was sent to the applicant requesting a response to the following:

*Table 3.2.P.3.4-1 states that the (b) (4) bulk product bioburden acceptance criterion ( (b) (4) is NMT (b) (4). This value appears high given that the bulk product can be held for up to 72 hours at room temperature (b) (4), and has natural antimicrobial properties. Please provide a justification for the value.*

An amendment response was received 05-OCT-2010.

**filename:** N200199r1.doc

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – Recommended for approval from a microbiology quality 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** – (b) (4)



- B. Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** - N/A.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Steven E. Fong, Ph.D.  
Microbiology Reviewer
- B. Endorsement Block** \_\_\_\_\_  
John Metcalfe, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**—N/A

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/s/

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STEVEN E FONG

10/18/2010

Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE

10/18/2010

I concur.

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 200-199/N-000 Applicant: Sandoz**

**Letter Date: 27-JAN-2010**

**Drug Name: Topotecan NDA Type: Standard**

**Stamp Date: 27-JAN-2010**

**Hydrochloride Injection**

**(tesamorelin acetate for injection)**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
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?	<b>X</b>		Application was submitted in eCTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	<b>X</b>		Manufacturing processes and microbiological controls described in sections 3.2.P.3.3 and 3.2.P.3.5, respectively.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	<b>X</b>		Environmental controls described in 3.2.P.3.3. (b) (4) processing controls described in section 3.2.P.3.5.
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?		<b>X</b>	Submission provided in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	<b>X</b>		Bacterial ingress studies presented in section G of a process validation report provided with submission.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	<b>X</b>		Sterility and endotoxin specifications presented in Table 3.2.P.5.1-1.
7	Has the applicant submitted the results of analytical method verification studies?	<b>X</b>		Sterility and endotoxin testing validations presented in sponsor documents VBM-36157_01 and VBM-36157_02.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	Pre-submission microbiology quality requests were not made.
9	Is this NDA fileable? If not, then describe why.	<b>X</b>		

Additional Comments: The drug product is to be manufactured at two sites: (b) (4), and Ebewe Pharma, Unterach, Austria (Establishment registration #3002829723).

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Steven Fong, Ph.D.  
Reviewing Microbiologist

Date

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David Hussong, Ph.D.  
Associate Director, New Drug Microbiology

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200199	ORIG-1	SANDOZ INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

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STEVEN E FONG  
04/28/2010

DAVID HUSSONG  
04/28/2010

The submission is filable.