# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203585Orig1s000

# MICROBIOLOGY REVIEW(S)

# Product Quality Microbiology Review

**August 30, 2012**

**NDA: 203585**

**Drug Product Name**
**Proprietary:** (Proposed) SYNRIBO
**Non-proprietary:** Omacetaxine Mepesuccinate

**Review Number:** 1

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

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 30 MAR 2012 | 30 MAR 2012 | 12 APR 2012 | 18 APR 2012 |
| 4 JUN 2012 | 4 JUN 2012 | N/A | N/A |
| 9 JUL 2012 | 10 JUL 2012 | N/A | N/A |

**Applicant/Sponsor**
**Name:** Cephalon, Inc.
**Address:** 41 Moores Road, P.O. Box 4011, Frazer, PA 19355
**Representative:** Carol Marchione
**Telephone:** 610-738-6237

**Name of Reviewer:** Erika Pfeiler, Ph.D.

**Conclusion:** Recommend approval

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** 505(b)(1)

**2. SUBMISSION PROVIDES FOR:** Initial marketing of a sterile drug product

**3. MANUFACTURING SITE:**

(b) (4)

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

- Lyophilized powder for injection in an 8 ml glass vial with stopper, single-use
- Subcutaneous injection, powder to be reconstituted with 1 ml 0.9% NaCl
- 3.5 mg/vial (final injectable concentration is 3.5 mg/ml)

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

**6. PHARMACOLOGICAL CATEGORY:** For treatment of accelerated phase CML in adult patients with resistance or intolerance to prior TKI therapy

**B. SUPPORTING/RELATED DOCUMENTS:** Microbiology Review 19 of DMF (b) (4), 9 December 2011

**C. REMARKS:** This application was submitted in the eCTD format.

Two information requests were communicated to the applicant via the RPM. Responses were received on June 4 and July 10, and incorporated into the relevant sections of the review.

(b) (4)

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*Container/closure integrity*

- The application references a dye ingress test for container closure integrity. Test methods for the dye ingress test used to examine container/closure integrity are not described. Please describe these test methods fully, including a description of the positive and negative controls used.

*Process validation*

- Please provide your requalification schedule for media fills.

(b) (4)

- Please provide methods and data from your most recent (b) (4) studies
- (b) (4)
- have any validation studies been performed to ensure that the process is adequate for a maximum load?
- The application does not contain information on the (b) (4) stoppers. Please describe (b) (4) provide a Letter of Authorization for the appropriate DMF for the validation studies.

*Analytical procedures*

- Please provide a detailed description of the analytical methods used for sterility testing. Be sure to include a description of method suitability testing performed.
- Provide a detailed description of the analytical methods used for endotoxin testing. Describe which technique listed in USP<85> is used, and describe inhibition/enhancement studies used to demonstrate that the method is suitable for use with the drug product.
- State the number of articles that will be tested for sterility and endotoxin in each production batch of drug product.

*Labeling*

- The draft package insert states that the product is stable at room temperature for up to (b) (4) after reconstitution. 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 proposed 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. Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ 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 (≤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.

<u>June 21 IR</u>

- Your application describes the dye ingress container closure integrity assessments that are performed on each batch of drug product (b) (4) Please provide validation data for the use of this method in assessing container closure integrity. (b) (4)

- In your June 4 response to the May 10 product quality microbiology information request, you describe methods used to test for the presence of endotoxins in the drug product. This submission

states that endotoxin specifications were NMT [redacted] (b) (4)
However, the endotoxin specifications in your original submission call for [redacted] (b) (4).
Please clarify your endotoxin specification.

**filename:** N203585R1.doc

# Executive Summary

**I. Recommendations**

**A. Recommendation on Approvability -** Recommend for approval on the basis of 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 –** (b) (4)

**B. Brief Description of Microbiology Deficiencies –** N/A

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

**III. Administrative**

**A. Reviewer's Signature _____**
Erika Pfeiler, Ph.D.

**B. Endorsement Block_____**
Bryan Riley, Ph.D.
Microbiology Team Leader

**C. CC Block**
N/A

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/s/

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ERIKA A PFEILER
08/30/2012

BRYAN S RILEY
08/30/2012
I concur.

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 203585 **Applicant:** Cephalon, Inc. **Letter Date:** March 30, 2012

**Drug Name:** Omacetaxine Mepesuccinate **NDA Type:** 505(b)(1) **Stamp Date:** March 30, 2012

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? | X | | |
| 2 | Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product? | X | | |
| 3 | Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product? | X | | A more thorough description of (b) (4) container/closure (b) (4) validation is needed. |
| 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? | X | | Executed batch record is in French. An English translation of the master batch record is provided. |
| 5 | Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies? | X | | Preservative effectiveness studies are not necessary for the product, but the container closure integrity study is not adequately described. |
| 6 | Has the applicant submitted microbiological specifications for the drug product and a description of the test methods? | X | | Test methods only reference USP<71> and USP<85> without an adequate description of how tests are carried out on the drug product. |
| 7 | Has the applicant submitted the results of analytical method verification studies? | X | | |
| 8 | Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions? | | | N/A |

| | Content Parameter | Yes | No | Comments |
|---|---|---|---|---|
| 9 | If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data? | | X | Proposed label includes a statement that drug product is stable for (b) (4) at room temperature after constitution, but provides no microbiological data to support this hold time. |
| 10 | Is this NDA fileable? If not, then describe why. | X | | |

**Additional Comments: N/A**

Erika Pfeiler, Ph.D.
Reviewing Microbiologist Date

Bryan Riley, Ph.D.
Microbiology Team Leader Date

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/s/

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ERIKA A PFEILER
05/14/2012

BRYAN S RILEY
05/14/2012
I concur.