

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-249

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

06 FEB 2008

NDA: 22-249-BC

Drug Product Name

Proprietary: Treanda® (proposed)
Non-proprietary: Bendamustine hydrochloride
Drug Product Priority Classification: 1P

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
07-JAN-2008	08-JAN-2008	08-JAN-2008	08-JAN-2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
19-SEP-2007	1	17-DEC-2007
15-NOV-2007	1	17-DEC-2007

Applicant/Sponsor

Name: Cephalon, Inc.
Address: 41 Moores Road
Frazer, PA 19355

Representative: Carol S. Marchione
Senior Director & Group Leader
Regulatory Affairs

Telephone: 610-738-6237
E-mail: cmarchio@cephalon.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Amendment to a new drug application
 2. **SUBMISSION PROVIDES FOR:** Responses to microbiology questions identified in Microbiology Review #1
 3. **MANUFACTURING SITE:** Pharmachemie B.V.
Swensweg 5
2003 RN Haarlem
The Netherlands
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Lyophilized powder in a 20 mL single-use glass vial
 - Intravenous infusion
 - 100 mg
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** Antineoplastic agent for treatment of patients with chronic lymphocytic lymphoma (CLL)
- B. **SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review #1 dated 17-DEC-2007
- C. **REMARKS:** This amendment is an electronic submission and is in response to 6 microbiology questions and 2 comments communicated to the applicant on 17-DEC-2007 (see DFS).

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – NDA 22-249 is 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 drug product is

/ / /
- 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**
Stephen E. Langille, Ph.D.
- C. CC Block**
N/A

6 Page(s) Withheld

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Draft Labeling

Deliberative Process

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/s/

Anastasia Lolos
2/6/2008 03:46:29 PM
MICROBIOLOGIST

Stephen Langille
2/6/2008 03:48:49 PM
MICROBIOLOGIST

Product Quality Microbiology Review

17 DEC 2007

NDA: 22-249

Drug Product Name

Proprietary: Treanda® (proposed)
Non-proprietary: Bendamustine hydrochloride
Drug Product Priority Classification: 1P

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
19-SEP-2007	20-SEP-2007	01-OCT-2007	01-OCT-2007
15-NOV-2007	16-NOV-2007	N/A	N/A

Submission History (for amendments only) – N/A

Applicant/Sponsor

Name: Cephalon, Inc.
Address: 41 Moores Road
Frazer, PA 19355

Representative: Carol S. Marchione
Senior Director and Group Leader
Regulatory Affairs

Telephone: 610-738-6237
E-mail: cmarchio@cephalon.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Approvable pending the resolution of product quality 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:** Pharmachemie B.V.
Swensweg 5
2003 RN Haarlem
The Netherlands
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Lyophilized powder in a 20 mL single-use glass vial
 - Intravenous infusion
 - 100 mg
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** Antineoplastic agent for treatment of patients with chronic lymphocytic lymphoma (CLL)
- B. **SUPPORTING/RELATED DOCUMENTS:**
- IND 67,554
 - OGD Microbiology Review #3 of DMF _____ (dated 01-AUG-2006);
was found adequate at _____
- C. **REMARKS:** This is an electronic submission in CTD format. This NDA has been selected as a pilot for the new GRMP process. The drug product has also obtained an orphan drug designation.

A completed filing checklist was entered in DFS on 18-OCT-2007. ONDQA's Initial Quality Assessment has identified product quality microbiology as a critical issue for final recommendation on this application.

An information request was sent to the applicant on 08-NOV-2007 to provide the following (identified during the filing review):

- _____
- _____
- _____

An amendment was submitted on November 15, 2007 and this information has been included in the relevant sections of the review.

file name: N022249R1.doc

Executive Summary**I. Recommendations**

- A. **Recommendation on Approvability** – NDA 22-249 is approvable pending the resolution of product quality microbiology deficiencies (see Section 3)
- 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 drug product is
_____ / _____ / _____
- B. **Brief Description of Microbiology Deficiencies** – Additional information is needed regarding the _____ studies and _____ validation studies.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Additional information is needed to assess the adequacy of certain sterilization processes, and as a result the sterility assurance of the product.

III. Administrative

- A. **Reviewer's Signature** _____
Anastasia G. Lolas
- B. **Endorsement Block**
Bryan S. Riley, Ph.D.
- C. **CC Block**
N/A

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Draft Labeling

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/s/

Anastasia Lolas
12/17/2007 10:10:04 AM
MICROBIOLOGIST

I revised it as we discussed.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-249

Applicant: Cephalon, Inc.

Letter Date: 19-SEP-2007

Drug Name: TREANDA®

NDA Type: 1P

Stamp Date: 20-SEP-2007

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		Results of studies are provided in a table format (no protocols or study reports, no dates). Sufficient detail is lacking in some cases.
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		All micro information is in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?		X	Studies not submitted for the _____ tests.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A		Micro did not participate in any pre-submission meetings.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: Missing information (#7) can be requested from the applicant as soon as possible. An information request will be prepared during the review period of this NDA to request additional detail on certain studies. The vial and carton labels

_____ The package insert _____

10/18/07

Anastasia G. Lolas, Reviewing Microbiologist

Date

Bryan S. Riley, Ph.D., Microbiology Secondary Reviewer

Date

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/s/

Anastasia Lolas
10/18/2007 02:10:42 PM
MICROBIOLOGIST

Bryan Riley
10/18/2007 02:11:50 PM
MICROBIOLOGIST