

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202714Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

07 May 2012

**NDA:** 202714/N-000

**Drug Product Name**

**Proprietary:**

**Non-proprietary:**

Carfilzomab for 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 SEP 2011	27 SEP 2011	04 OCT 2011	6 OCT 2011
20 DEC 2011	21 DEC 2011	N/A	N/A

**Applicant/Sponsor**

**Name:**

Onyx Pharmaceuticals, Inc.

**Address:**

249 E. Grand Ave.

South San Francisco, CA 94080

**Representative:**

Sheldon Mullins

**Telephone:**

650-266-1033

**Name of Reviewer:**

John W. Metcalfe, Ph.D.

**Conclusion:**

Recommend approval.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** A 505 (b)(1) NDA.
  2. **SUBMISSION PROVIDES FOR:** Marketing authorization.
  3. **MANUFACTURING SITE:**  
 (b)(4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Lyophilized powder in  vial.
    - Intravenous injection.
    - 60 mg/vial.
  5. **METHOD(S) OF STERILIZATION:**  (b)(4)
  6. **PHARMACOLOGICAL CATEGORY:** The drug product is indicated for the treatment of relapsed and refractory multiple myeloma.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review of DMF  (b)(4) dated 06 September 2011.
  - Microbiology Review of DMF  (b)(4) dated 07 May 2012.

C. **REMARKS:**

The subject NDA is submitted electronically in CTD format.

The following microbiology comment was forwarded to the applicant by the OND Project Manager in the 74 day letter on 08 December 2011:

Reference is made to Section 2.6 (*Reconstitution and Preparation for Intravenous Administration*) of the draft label. The following comment is provided in response to your plan to allow a  (b)(4) holding time at room temperature between reconstitution of the final drug product and patient administration:

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 at room temperature. 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.

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

The applicant amended the NDA with a response to this comment on 21 December 2011. The response indicated that the label will be changed to state that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours at refrigerated temperature.

**File Name:** N202714R1.doc

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – NDA 202714/N-000 is recommended for approval on the basis of issues pertaining to product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - The bulk drug solution is

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers the text of item A under section II.

- B. Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
John W. Metcalfe, Ph.D.
- B. Endorsement Block** \_\_\_\_\_  
Stephen E. Langille, Ph.D.
- C. CC Block**  
N/A

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/s/  
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JOHN W METCALFE  
05/08/2012

STEPHEN E LANGILLE  
05/08/2012

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 202714.

**Applicant:** Onyx  
Pharmaceuticals, Inc.

**Letter Date:** 27 SEP 2011.

**Drug Name:** Carfilzomib (PR-171) for Injection.    **NDA Type:** 505 (b)(1).

**Stamp Date:** 27 SEP 2011.

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		Module 3.2.P.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Reference is made to DMF (b)(4) for the validation of the manufacturing process.
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	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		The drug product is not preserved. CCI studies are provided in Module 3.2.P.2.5.1.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3.2.P.5.1.
7	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?		X	This reviewer is unaware of any requested information prior to submission of the NDA.
9	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:** Reference is made to the Reviewer's Comment on Page 2.

\_\_\_\_\_  
John W. Metcalfe, Ph.D.  
Senior Microbiology Reviewer, CDER/OPS/NDMS.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Bryan S. Riley, Ph.D.  
Senior Microbiology Reviewer, CDER/OPS/NDMS.

\_\_\_\_\_  
Date

## **Review Notes**

The subject drug product is a lyophilized powder to be reconstituted with Sterile Water for Injection, USP. The diluent is not provided with the drug product. Once reconstituted, the drug product may be administered directly, or diluted into a bag of 5% Dextrose Injection, USP (D5W). The draft label states that the product is stable at refrigerated temperature for 24 hours in the vial, syringe or D5W IV bag; and at room temperature for (b) (4) in the vial, 4 hours in the syringe or (b) (4) in the D5W bag. Finally, the draft label states, "Total time from reconstitution to administration should not exceed 24 hours." However, the application does not contain microbiological data in support of these post reconstitution holding periods.

## **Reviewer's Comment**

The following comment and Information Request should be forwarded to the applicant:

Reference is made to Section 2.6 (*Reconstitution and Preparation for Intravenous Administration*) of the draft label. The following comment is provided in response to your plan to allow a (b) (4) holding time at room temperature between reconstitution of the final drug product and patient administration:

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 at room temperature. 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.

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**END**

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/s/  
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JOHN W METCALFE  
11/04/2011

BRYAN S RILEY  
11/04/2011  
I concur.