

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

25 March 2013

NDA: 203-971/N000

Drug Product Name

Proprietary: Xofigo

Non-proprietary: radium Ra 223 dichloride

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
14 December 2012	14 December 2012	14 December 2012	14 December 2012
21 January 2013 (SD 07)	22 January 2013	NA	NA
22 February 2013 (SD 21)	25 February 2013	NA	NA

Submission History (for amendments only) – NA

Applicant/Sponsor

Name: Bayer HealthCare Pharmaceuticals, Inc.

Address: 340 Changebridge Rd
Pinebrook, NJ 07058

Representative: Deepika Jalota, Pharm. D.
Deputy Director, Regulatory Affairs

Telephone: (973) 487-2782

Name of Reviewer: Denise A. Miller

Conclusion: Recommend to approve from a quality microbiology perspective.

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUBMISSION:** Original Application
 2. **SUBMISSION PROVIDES FOR:** The manufacture and marketing for the radiopharmaceutical drug product Xofigo.
 3. **MANUFACTURING SITE:**
Institute for Energy Technology
Instituttveien 18
PO Box 40
Kjeller Norway NO-2027
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Dosage Form: Sterile solution; 6 mL fill in a 10mL vial.
 - Route of Administration: Intravenous
 - Strength/Potency: 1000 kBq/mL (0.027 mCi/mL) at reference date
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Radiopharmaceutical treatment for castration-resistant prostate cancer patients with bone metastases.
- B.**
- SUPPORTING/RELATED DOCUMENTS:**
- DMF (b) (4) Type III (b) (4) (b) (4)
LOA September 19, 2012 references submission July 18, 2012. DMF (b) (4) lists (b) (4)
- (b) (4) An information request was sent to the NDA sponsor asking for clarification of which (b) (4) they are using. The sponsor responded on 01/21/13 stating that the manufacturing process would use (b) (4) DMF review dated 08 March 2013 was acceptable and is supportive of this NDA.
- DMF (b) (4) Type II (b) (4) LOA dated 07/13/2012 referencin (b) (4)
- (b) (4) The referenced submission was reviewed by OGD on 12/13/11 and determined to be adequate. DMF (b) (4) is supportive of this NDA.
- C.**
- REMARKS:**
- 1) Application is in e-CTD format.
 - 2) As this product is (b) (4) this review concentrated on the (b) (4) the container closure integrity, endotoxin release testing, and the (b) (4) validation for the stoppers and vials.

3) An information request was sent on 14 December 2012 for clarification of which vials are to be used. A response was received on 22 January 2013.

4) IR #2 was sent on 04 February 2013 requesting additional information on the (b) (4) process and the container closure integrity testing. A response was received on 25 February 2013.

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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 radioactive product is filled into 10 mL vials (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** _____
John W. Metcalfe, Ph.D.
Senior Microbiologist, OPS/NDMS
- C. CC Block**
N/A

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/s/

DENISE A MILLER
03/26/2013

JOHN W METCALFE
03/26/2013
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203-971

Applicant: Bayer

Letter Date: 12/14/12

Drug Name: Xofigo

NDA Type: 505(b)(1)

Stamp Date: 12/14/12

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?		√	(b) (4) studies not included. DMFs were referenced for (b) (4).
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?	√		PE not required CCI testing included
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	If sterile, are extended post-constitution and/or post-dilution hold time in the draft labeling supported by microbiological data?	NA		Drug is not diluted or reconstituted.
10	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:

This drug product is (b) (4) There is a Letter of Authorization (LOA) referenced for Type III DMF (b) (4) for the (b) (4). There is also a LOA that references Type III DMF (b) (4) for the (b) (4). The (b) (4) listed in DMF (b) (4)

The sponsor should clarify which (b) (4) they are using.

Information Request: DMF (b) (4) is referenced for the (b) (4) to be used for Xofigo. This DMF lists (b) (4) Clarify which (b) (4) are to be used.

Denise A. Miller, Microbiologist

Date

John W. Metcalfe, Ph.D.

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE A MILLER
01/08/2013

JOHN W METCALFE
01/08/2013
I concur.