CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

09 April 2012

NDA: 202207/N-000

Drug Product Name
Proprietary: Lymphoseek.
Non-proprietary: Tilmanocept.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10 AUG 2011	10 AUG 2011	12 AUG 2011	18 AUG 2011
06 JAN 2012	06 JAN 2012	N/A	N/A
17 FEB 2012	17 FEB 2012	N/A	N/A

Applicant/Sponsor
Name: Navidea Biopharmaceuticals, Inc.
Address: 425 Metro Place North
Suite 450
Dublin, OH 43017
Representative: Roger A. Brown
Telephone: 614-822-2342.

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

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

2. SUBMISSION PROVIDES FOR: Marketing authorization.

3. MANUFACTURING SITE:

Drug Product	Diluent
(b) (4)	

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

Drug

- Lyophilized powder for Injection in 5 mL glass vial.
- (b) (4) injection.
- 0.25 mg per vial.

Diluent

- Sterile Buffered Saline in glass vial.
- 4.5 mL/vial.

5. METHOD(S) OF STERILIZATION:

- Drug Product: (b) (4)
- Diluent: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Radiopharmaceutical Imaging Agent.

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review of (b) (4); dated 02 April 2012.
- Microbiology Review of DMF (b) (4); dated 05 April 2011.

C. REMARKS:

The subject NDA was submitted electronically in the CTD format.

The NDA contains a Letter of Authorization from (b) (4) (dated 22 March 2011) for reference to its (b) (4) regarding manufacture of the diluent. This Master File is held in CBER.

A Microbiology Information Request was submitted to the applicant on 13 December 2011 by the OND Project Manager. Following is the request for information:

A microbiology review of NDA 202207 is in progress.

Comment #1.
Reference is made to USP<85> which states that the endotoxin limit for radiopharmaceutical products is 175/V, where V is the maximum recommended dose in mL. Reference is also made to Tables 1 and 2 of Module 3.2.P.5.1 of NDA 202207 which states that the limit for bacterial endotoxins is NMT (b) (4) for the lyophilized product and (b) (4) for the diluent.

It is unclear from your draft label what the number of vials is that will be required to formulate a maximum patient dose. If more than one product and diluent vial are required to prepare a dose, then the patient may potentially receive a higher amount of endotoxin than what is allowed in USP. In addition, the endotoxin limit stated in USP represents that which is allowable of the final drug product for patient administration, which is comprised of both the lyophilized product and its diluent.

- Provide the maximum number of vials that will be used to prepare a patient dose.
- Modify the bacterial endotoxins limit to be consistent with what is allowed in USP, taking into account the final product for administration (combination of lyophilized powder and diluent) as well as the number of product vials required to formulate a maximum patient dose.

Comment #2.
Reference is made to Table 2 of Module 3.2.P.3.3.9 which states that the (b) (4) (b) (4) bioburden acceptance criterion is (b) (4). This criterion is (b) (4). For comparison, reference is made to USP<1231> which suggests that Water for Injection not contain > 10 CFU/100 mL. Your manufacturing process should not add a significant level of bioburden to the action level for WFI.

- Amend the application with a (b) (4) bioburden limit which is closer to the USP recommendation for Water for Injection.

Comment #3.
Reference is made to Module 3.2.P.3.5.3.4 which summarizes the bacterial retention validation studies for the (b) (4) The application states that "the (b) (4) validation file is available for inspection at (b) (4) and Neoprobe", however this file was not provided in the NDA.

- Amend the application with the stated (b) (4) validation file.

The applicant amended the NDA with responses to this IR on 06 January 2012. The responses are summarized and reviewed in appropriate sections of this review.

This reviewer also performed a review of (b) (4) to assess the sterility assurance regarding the diluent to be packaged with the lyophilized powder. During the review of the subject master file, this reviewer requested additional information from the master file holder and further requested that the information be amended to the subject NDA to facilitate an expedient review, as compared to amending the master file. On 17 February 2012 the requested diluent information was amended to the subject NDA, and is reviewed in appropriate sections of this review.

File Name: N202207N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 202207/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 – Both the drug product and diluent are manufactured by (b) (4) processing.

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_____
Bryan S. Riley, Ph.D.

C. CC Block
N/A

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/s/

JOHN W METCALFE
04/09/2012

BRYAN S RILEY
04/09/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 202207. **Applicant:** Neoprobe Corp. **Letter Date:** 10 August 2011.

Drug Name: Lymphoseek. **NDA Type:** 505(b)(1). **Stamp Date:** 10 August 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		Drug Product (DP) manufacturing process and in process controls: 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		Drug Product Sterilization Validation: Module 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?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		DP CCI: Module 3.2.P.2.4.5. Preservative Effectiveness: N/A.
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.3.5.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not Applicable. This reviewer is unaware of any pre-submission information requests.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:
The drug product is packaged with a diluent (sterile buffered saline) which is manufactured at (b) (4) . The NDA contains a Letter of Authorization from (b) (4) allowing for review of the subject DMF (b) (4) which is located in CBER. Although this reviewer initially requested the DMF on 02 September 2011, it has not been provided at the time of completion of this microbiology filing review.

John W. Metcalfe, Ph.D. Date

Bryan S. Riley, 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/

JOHN W METCALFE
09/15/2011

BRYAN S RILEY
09/15/2011
I concur.