CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

17 JUNE 2009

NDA: 22-288/N-000

Drug Product Name
Proprietary: Bepreve™
Non-proprietary: Bepotastine besilate ophthalmic solution.
Drug Product Priority Classification: S.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
12 NOV 2008	12 NOV 2008	17 NOV 2008	20 NOV 2008
03 JUN 2009	03 JUN 2009	N/A	N/A

Applicant/Sponsor
Name: ISTA Pharmaceuticals®, Inc.
Address: 15295 Alton Parkway
Irvine, CA 92618
Representative: Paul Nowacki
Telephone: 949-789-3109

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

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA.

2. SUBMISSION PROVIDES FOR: A new drug product.

3. MANUFACTURING SITE:
(b) (4)

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

- Solution in LDPE dropper bottle.
- Topical ophthalmic.
- 1.5%.

5. METHOD(S) OF STERILIZATION: Sterile filtration followed by (b) (4).

6. PHARMACOLOGICAL CATEGORY: The drug product is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:
The NDA is submitted electronically in the CTD format.

As of 13 January 2009 there is no ONDQA Initial Quality Assessment in DFS.

An information request was forwarded by this reviewer to the OND project manager for dissemination to the applicant on 15 May 2009. Following is the information request:

> A sterility assurance review of NDA 22-288 is on-going. Please address the following comments:
>
> - Section 4.2 of *Process Validation Plan: 1.5% Bepotastine Besilate Ophthalmic Solution* (Module 3.2.P.3.3) states the following:
>
>> "A bulk solution hold study will be performed to demonstrate that the bulk solution can be held for a predetermined length of time (e.g. multiple days) and will meet chemistry and bioburden specifications. The hold time for the sterile filtered bulk solution will also be validated."

Provide the holding times and supporting data/rationale for the bulk solution prior to filtration and the sterile solution prior to filling.

(b) (4)

The applicant amended the NDA on 03 June 2009 with responses to this information request. The applicant responses are summarized and reviewed in appropriate sections of this review.

File Name: N022288R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-288/N-000 is recommended for approval on the basis of issues pertaining to sterility assurance.

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 - Following compounding, the bulk drug solution is sterilized [redacted] (b) (4)

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 Langille, Ph.D.

C. CC Block
N/A

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/s/

John Metcalfe
6/17/2009 02:06:27 PM
MICROBIOLOGIST

Stephen Langille
6/17/2009 02:07:15 PM
MICROBIOLOGIST

Deliverables by Mid-Cycle for Product Quality Microbiology

(1) Team participation requested, submission received and assigned to Microbiology reviewer (by day 21).

(2) Microbiology reviewer performs filing review and a preliminary review of draft labeling (by day 45).

(3) Microbiology reviewer completes the filing checklist and identifies filing issues and/or other major deficiencies. Checklist is signed off in DFS by secondary reviewer/Team Leader (by day 45).

(4) When potential fileability issues or serious deficiencies are identified, the Microbiology reviewer attends the filing meeting and presents the filing issues and/or deficiencies to be communicated to the applicant.

(5) First review completed prior to mid-cycle meeting with secondary reviewer's concurrence. Information request sent soon after completion of the first review (by month 5).

(6) Microbiology reviewer attends appropriate team meetings and the mid-cycle meeting and presents findings accordingly.

(7) Reviewer and secondary reviewer/Team Leader communicate frequently regarding the review status, submission data and deficiencies.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-288 **Applicant:** Ista Pharmaceuticals®, Inc. **Letter Date:** 12 NOV 2008

Drug Name: Bepreve™ Bepotastine besilate ophthalmic solution **NDA Type:** Standard **Stamp Date:** 12 NOV 2008

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		
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		
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		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			I am unaware of any pre-submission special studies/data that were requested.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: None.

John W. Metcalfe, Ph.D. 09 DEC 2008

Reviewing Microbiologist Date

Stephen Langille, Ph.D.

Microbiology Secondary Reviewer/Team Leader 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 Metcalfe
12/17/2008 07:44:01 AM
MICROBIOLOGIST

Stephen Langille
12/18/2008 09:28:00 AM
MICROBIOLOGIST