

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

17 JAN 2012

NDA: 202-514

Drug Product Name

Proprietary: Zioptan

Non-proprietary: Tafluprost, preservative-free

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
13 JAN 2012	13 JAN 2012	14 JAN 2012	14 JAN 2012

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
07 JAN 2011	1	30 SEPT 2011
09 FEB 2011	1	30 SEPT 2011
29 MAR 2011	1	30 SEPT 2011
08 JUN 2011	1	30 SEPT 2011
01 AUG 2011	1	30 SEPT 2011
22 AUG 2011	1	30 SEPT 2011
06 SEPT 2011	1	30 SEPT 2011
13 SEPT 2011	1	30 SEPT 2011
27 SEPT 2011	1	30 SEPT 2011
27 OCT 2011	2	04 NOV 2011
02 NOV 2011	2	04 NOV 2011

Applicant/Sponsor

Name: Merck Sharp and Dohme Corp.

Address: 126 E. Lincoln Ave.
PO Box 2000
Mail Drop RY33-204
Rahway, NJ 07065-0900

Representative: Chitkala Kalidas, Ph.D.

Telephone: 732-594-0599

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: This application is recommended for approval.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Class I resubmission of a 505 (b)(1) NDA
2. **SUBMISSION PROVIDES FOR:** Complete response to the approvable letter dated 07 November 2011 for a new preservative-free topical ophthalmic drug product.
3. **MANUFACTURING SITE:** Laboratoire Unither
ZI de la Guerie
F-50211 Coutances Cedex
France
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Preservative-free ophthalmic solution
 - 0.0015% tafluprost
 - Single dose ampules for topical ocular administration
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.
- B. **SUPPORTING/RELATED DOCUMENTS:** Product Quality Microbiology Review #1 dated 30 September 2011 and Review #2 dated 04 November 2011. Also see the Director's Memorandum of Concurrence dated 04 November 2011.
- C. **REMARKS:** This submission was in the eCTD format.

filename: N202514R3.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This application is recommended for approval on the basis of 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** – This is a non-preserved aqueous solution that is (b) (4) into single-use containers (b) (4).
- B. Brief Description of Microbiology Deficiencies** – Not applicable.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, Ph.D.
- B. Endorsement Block** _____
John Metcalfe, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

JESSICA COLE
01/18/2012

JOHN W METCALFE
01/18/2012
I concur.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4 November 2011

TO: NDA 202-514 Tafluprost

FROM: David Hussong, Ph.D., Associate Director for New Drug Microbiology, OPS

CC: Renata Albrecht, MD, Director, Division of Transplant and Ophthalmology Products

SUBJECT: Director's Memorandum of Concurrence with Review Recommendation

The microbiology review of NDA 202-514 (Tafluprost ophthalmic drops) has noted that the sterile manufacturing process validation studies (b) (4) were flawed. The manufacturer had been using a procedure that discards failed test units on the basis of reevaluation. Generally, this practice would be viewed as "testing into compliance," and is an undesirable practice as detailed in the agency's Guidance on (b) (4) processing. It is important to consider that the compendial sterility test procedure will only detect contamination less than 35% of the time even when the portion of contaminated samples exceeds (b) (4). Therefore, complete validation is critical to sterility assurance.

The applicant has provided a commitment to perform appropriate (b) (4) but only by the end of (b) (4). This would mean that approval of the application could permit marketing of product prior to a complete demonstration of sterile manufacturing capability. We wanted to allow the applicant the opportunity to complete the validation and begin drug manufacture as promptly as possible, and proposed that the approval would be conditioned upon a commitment to withhold shipment of product until the validation was complete. However, that condition cannot be enforced in a post-approval commitment. If the applicant chose to market the product and subsequently (b) (4) failed (b) (4), the outcomes should be considered.

1. All marketed product could be recalled for lack of sterility assurance.
2. Patients might be exposed to contaminated products. Bacteria capable of growing in the solution would have time to reach great populations.
3. The Quality Assurance department may exercise its authority to investigate the cause of the failure and conclude there is no risk. Their conclusion may be subject to bias.

Two of these outcomes are undesirable from a regulatory and safety perspective. Based on these considerations and the applicant's lack of willingness to perform these studies in a more timely fashion, I conclude that the application should not be approved until three

MEMORANDUM

consecutive (b) (4) are completed successfully and reported to the application file.

Recommendation: The application is approvable pending completion of the sterile process validation studies.

The following deficiency should be conveyed to the applicant.

Provide a report of studies that include the results of three consecutive successful (b) (4) processing simulations of the Zioptan manufacturing process (b) (4) using the revised inspection and accounting procedures.

END

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/s/

DAVID HUSSONG
11/04/2011

Product Quality Microbiology Review

04 NOV 2011

NDA: 202-514

Drug Product Name

Proprietary: Zioptan (proposed)

Non-proprietary: Tafluprost, preservative-free

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
27 OCT 2011	27 OCT 2011	26 OCT 2011	03 NOV 2011
02 NOV 2011	02 NOV 2011	03 NOV 2011	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
07 JAN 2011	1	30 SEPT 2011
09 FEB 2011	1	30 SEPT 2011
29 MAR 2011	1	30 SEPT 2011
08 JUN 2011	1	30 SEPT 2011
01 AUG 2011	1	30 SEPT 2011
22 AUG 2011	1	30 SEPT 2011
06 SEPT 2011	1	30 SEPT 2011
13 SEPT 2011	1	30 SEPT 2011
27 SEPT 2011	1	30 SEPT 2011

Applicant/Sponsor

Name: Merck Sharp and Dohme Corp.

Address: 126 E. Lincoln Ave.
PO Box 2000
Mail Drop RY33-204
Rahway, NJ 07065-0900

Representative: Chitkala Kalidas, Ph.D.

Telephone: 732-594-0599

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Approvable pending successful completion of
(b) (4) process validation studies.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original 505 (b)(1) NDA
 - 2. SUBMISSION PROVIDES FOR:** New preservative-free topical ophthalmic drug product.
 - 3. MANUFACTURING SITE:** Laboratoire Unither
ZI de la Guerie
F-50211 Coutances Cedex
France
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Preservative-free ophthalmic solution
 - 0.0015% tafluprost
 - Single dose ampules for topical ocular administration
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.
- B. SUPPORTING/RELATED DOCUMENTS:** Product Quality Microbiology Review #1 dated 30 September 2011.
- C. REMARKS:** This submission was in the eCTD format.

filename: N202514R2.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Approvable pending completion of (b) (4) process validation studies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – There are no product quality microbiology phase 4 commitments.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a non-preserved aqueous solution that is (b) (4) into single-use containers (b) (4).
- B. Brief Description of Microbiology Deficiencies** – The deficiencies from review #1 have been corrected but the revised (b) (4) validation studies are not scheduled to be complete until 1Q 2012.
- C. Assessment of Risk Due to Microbiology Deficiencies** – There is a moderate risk of release of non-sterile product; however, without adequate validation studies it is difficult to accurately assess the safety risk.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

JESSICA COLE
11/04/2011

STEPHEN E LANGILLE
11/04/2011
I concur.

DAVID HUSSONG
11/04/2011

The microbiology review of NDA 202-514 (Tafluprost ophthalmic drops) has noted that the sterile manufacturing process validation studies (b) (4) were flawed. The manufacturer had been using a procedure that discards failed test units on the basis of reevaluation. Generally, this practice would be viewed as testing into compliance, and is an undesirable practice as detailed in the agency's Guidance on (b) (4) processing. I conclude that the application should not be approved until three consecutive (b) (4) are completed successfully and reported to the application file. A concurrence memorandum will be filed separately.

Product Quality Microbiology Review

29 SEP 2011

NDA: 202-514

Drug Product Name

Proprietary: Zioptan (proposed)

Non-proprietary: Tafluprost, preservative-free

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
07 JAN 2011	07 JAN 2011	10 FEB 2011	11 FEB 2011
09 FEB 2011	09 FEB 2011	N/A	N/A
29 MAR 2011	29 MAR 2011	N/A	N/A
08 JUN 2011	08 JUN 2011	N/A	N/A
01 AUG 2011	01 AUG 2011	N/A	N/A
22 AUG 2011	22 AUG 2011	N/A	N/A
06 SEPT 2011	06 SEPT 2011	N/A	N/A
13 SEPT 2011	13 SEPT 2011	N/A	N/A
27 SEPT 2011	27 SEPT 2011	N/A	N/A

Applicant/Sponsor

Name: Merck Sharp and Dohme Corp.

Address: 126 E. Lincoln Ave.
PO Box 2000
Mail Drop RY33-204
Rahway, NJ 07065-0900

Representative: Chitkala Kalidas, Ph.D.

Telephone: 732-594-0599

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Approvable pending resolution of microbiology deficiencies on page 16.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original 505 (b)(1) NDA
 2. **SUBMISSION PROVIDES FOR:** New preservative-free topical ophthalmic drug product.
 3. **MANUFACTURING SITE:** Laboratoire Unither
ZI de la Guerie
F-50211 Coutances Cedex
France
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Preservative-free ophthalmic solution
 - 0.0015% tafluprost
 - Single dose ampules for topical ocular administration
 5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
[REDACTED].
 6. **PHARMACOLOGICAL CATEGORY:** Indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:** This submission was in the eCTD format. No information on the drug substance was provided in the original submission but can be found in the 9 February 2011 amendment. The endotoxin specification and test method can be found in the 22 August 2011 amendment.

The following comments were included in the 74-day letter. A response was received on 29 March 2011.

1. Provide the sterility test method and the results of validation studies. A detailed summary would also be acceptable.
2. Provide a description of the [REDACTED] (b) (4)
[REDACTED]
3. Provide the referenced media challenge results in support of the [REDACTED] (b) (4)
[REDACTED]
4. Please establish an endotoxin specification and submit the test method and validation studies.

The following information request was sent to the project manager on 25 April 2011 and a response was received on 08 June 2011 and 01 August 2011. The responses are incorporated into the relevant sections of this review.

1. Indicate whether the drug substance undergoes microbial limits testing upon receipt.
2. Filter validation studies (b) (4)
3. Describe how your (b) (4)
4. Provide evidence (b) (4)
5. Provide a diagram which provides the location of (b) (4)
6. Provide 3 (b) (4)
7. Provide a rationale for accepting (b) (4)
8. Clarify your (b) (4) procedure with respect to product inspection. Provide data to support that (b) (4).
9. Confirm that (b) (4) units are inspected as would occur during routine production and that if a positive unit is identified no additional inspection will occur to reject that positive unit.
10. Confirm that there is a (b) (4)
 Clarify these two contradictory descriptions of the manufacturing process.
11. Provide the results from sterility test validation studies which demonstrate the adequacy of your test method for this bactericidal product. We note your previous reference to Ph.Eur (b) (4) and your failure to submit the product-specific validation studies. Indicate what types of organisms are killed and what types of organisms have reduced growth properties in your product.

The following information request was sent to the project manager on 26 August 2011 and partial responses were received on 06, 13, and 27 September 2011.

1. (b) (4)
2. It is not possible to fully assess the bacterial retention studies conducted for the sterilizing (b) (4) based on the information provided (b) (4)
 Provide a comparison of the routine

filtration parameters used for production and the bacterial retention validation studies for the sterilizing (b) (4).

3. Provide the following information for the three process validation (b) (4)
(b) (4)
4. Revise the (b) (4) procedure to remove the additional inspection of positive vials after incubation. We refer to the 08 June 2011 amendment answer to question 9. (b) (4) should mimic production conditions and should not subject positive vials to additional scrutiny above that used for commercial product.
5. Describe the (b) (4)
(b) (4)
6. Information found in the 22 August 2011 amendment indicates that the production stability program does not include (b) (4)
(b) (4)

filename: N202514R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Approvable pending resolution of product quality microbiology deficiencies listed on page 16.
- 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** – This is a non-preserved aqueous solution that is (b) (4) into single-use containers (b) (4).
- B. Brief Description of Microbiology Deficiencies** – The (b) (4) processing validation studies (b) (4) are not sufficient to provide adequate sterility assurance for this drug product.
- C. Assessment of Risk Due to Microbiology Deficiencies** – There is a moderate risk for the release of non-sterile drug product.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

JESSICA COLE
09/30/2011

STEPHEN E LANGILLE
09/30/2011

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 202-514

Applicant: Merck

Letter Date: 7 January 2011

Drug Name: Saflutan
(Tafluprost, preservative-free)

NDA Type: 505(b)(1)

Stamp Date: 7 January 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		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		(b) (4) Bioburden is assessed.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	No information was provided on the sterilization (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?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		(b) (4) studies were provided.
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	The applicant references Ph.Eur for the sterility test validation studies.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This NDA is for a sterile, preservative-free, ophthalmic solution (b) (4) into single dose containers. There is no endotoxin limit provided in the specification; however this drug product is proposed for topical ophthalmic use and is not required to be apyrogenic. WFI is monitored for endotoxins. At the filing meeting the clinical division asked that an endotoxin specification be established.

Comments to be forwarded to the applicant:

1. Provide the sterility test method and the results of validation studies. A detailed summary would also be acceptable.

2. Provide a description of the [redacted] (b) (4)
3. Provide the referenced [redacted] (b) (4) challenge results in support [redacted] (b) (4)
4. Please establish an endotoxin specification and submit the test method and validation studies.

Jessica Cole 14 February 2011
Reviewing Microbiologist Date

Stephen Langille Date
Microbiology Secondary Reviewer

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/s/

JESSICA COLE
02/18/2011

STEPHEN E LANGILLE
02/18/2011