

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202667Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

AUGUST 09, 2011

**NDA:** 202667

**Drug Product Name**

**Proprietary:** COSOPT® Preservative Free Ophthalmic Solution

**Non-proprietary:** Dorzolamide hydrochloride and timolol maleate

**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>
February 16, 2011	February 16, 2011	February 18, 2011	February 24, 2011

**Submission History (for amendments only) – N/A**

**Applicant/Sponsor**

**Name:** Merck Sharp & Dohme Corporation  
**Address:** 126 E. Lincoln Avenue, P.O. Box 2000  
Rahway, NJ 07065-0900  
**Representative:** Chitkala Kalidas, Ph.D., Director,  
Worldwide Regulatory Affairs.  
**Telephone:** 732-594-0599

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** The application is recommended for approval from product quality microbiology standpoint.

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## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original NDA
  - 2. SUBMISSION PROVIDES FOR:** A new formulation which eliminates benzalkonium chloride as preservative from an approved drug product Cosopt®.
  - 3. MANUFACTURING SITE:** Laboratories Merck, Sharp and Dohme  
Chibret, Mirabel Plant  
France, CFN – FCFR252
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Ophthalmic Solution
    - ❖ Topical
    - ❖ Dorzolamide 2.0%; Timolol 0.5%
    - ❖ In a unit dose LDPE pipette
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Treatment of elevated intraocular pressure.
- B. SUPPORTING/RELATED DOCUMENTS:** NDA 20-869/S008, NDA 18-086/S054
- C. REMARKS:** The subject NDA 202667 is for a previously marketed drug product but without a preservative. This NDA submission contains cross-references to data submitted as part of three NDAs previously submitted by Merck to the FDA. They include the NDA submissions for the COSOPT® (NDA 20,869), TRUSOPT® (NDA 20,408) and TIMOPTIC® (NDA 18,086). Merck is the NDA holder for COSOPT® and TRUSOPT®. However, the rights to the NDA for TIMOPTIC® are currently owned by Aton Pharma and a Letter of Authorization from Aton Pharma is submitted in module 1.4.4 of the CTD. The subject NDA is essentially NDA 20-869 for COSOPT® minus the preservative. This is an electronic submission.

**filename:** N202667R1

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** – Recommended for approval.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This submission is based on a formulation change to eliminate benzalkonium chloride as a preservative. There are no changes in the manufacturing process which consists of (b) (4) which fills single-dose container strips called pipettes which are overwrapped in protective (b) (4) foil pouches.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER
- B. Endorsement Block** \_\_\_\_\_  
Bryan S. Riley, Ph.D., NDMS, OPS, CDER
- C. CC Block**  
N/A

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/s/  
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VINAYAK B PAWAR  
08/10/2011

BRYAN S RILEY  
08/10/2011  
I concur.

MEMORANDUM



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

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**DATE:** June 22, 2011

**TO:** Alison K. Rogers, Senior Regulatory Health Project Manager, CDER/DAIOP

**FROM:** Vinayak B. Pawar, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS

**THROUGH:** Bryan S. Riley, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS

**SUBJECT:** OPS Microbiology Review of Sponsor's Response to IR Letter dated April 19, 2011.

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**NDA:** 202667

**DRUG NAME:** Dorzolamide hydrochloride and Timolol Maleate Ophthalmic Solution.

**SPONSOR:** Merck Sharp & Dohme Corporation.

**LETTER DATE:** February 16, 2011

**RECEIPT DATE:** February 16, 2011

**Background:**

In the Product Quality Microbiology Filing Review of NDA 202667 dated March 23, 2011, the sponsor was sent an additional comment regarding the lack of bacterial endotoxins specification in this submission. This comment together with additional CMC questions were sent to the sponsor in an Information Request Letter dated April 19, 2011. The comment and the sponsor's response dated May 27, 2011 are provided below: Agency's Product Quality Microbiology Response follows.

**Comment:**

**3. Test the drug product for endotoxins at release and on stability, at least annually.**

**Sponsor's Response:**

The applicant believes that bacterial endotoxin testing is not a necessary test for Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free Ophthalmic Solution. Endotoxins produce a pyrogenic reaction and in severe cases septic shock when injected. As described in the proposed product labeling, Dorzolamide Hydrochloride (+) Timolol Maleate Preservative Free Ophthalmic Solution is administered to the intact surface of the eyeball and [REDACTED] (b) (4) [REDACTED] the patient would not be exposed to such a reaction.

Currently, bacterial endotoxin is not a critical quality attribute for sterile ophthalmic solutions as shown in USP <1151> "Pharmaceutical Dosage Forms" and the sponsor proposed specifications without endotoxin testing is in alignment with this compendial standard. This is further reinforced by the observation that there are approximately 80 USP monographs for sterile ophthalmic solutions and suspensions without bacterial endotoxin requirements.

**FDA Response:**

## MEMORANDUM

It is the policy of the ophthalmic review division that endotoxin should be controlled in topical ophthalmic products. Therefore, it recommended that applicants include an endotoxin specification for topical ophthalmic products targeted at an acceptance level of (b) (4)

**END**

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/s/  
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VINAYAK B PAWAR  
06/24/2011

BRYAN S RILEY  
06/24/2011  
I concur.

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 202667

**Applicant:** Merck Sharp & Dohme Corporation

**Letter Date:** February 16, 2011

**Drug Name:** Dorzolamide

**NDA Type:** Original

**Stamp Date:** February 16, 2011

Hydrochloride and Timolol  
Maleate ophthalmic Solution

*This drug product is identical to the previously marketed Cosopt® (NDA 20, 869) except for the lack of preservative and will be manufactured at the same Merck facility in Chibret, France.*

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		Section 3.2.P.3.3 Flow diagram in Figure 3.2.P.3.3-0507a
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.2.P.3.5 (Doc: February 11, 2011)
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		Preservative Effectiveness studies – N/A
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.5.1. (see additional comments)
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?			N/A
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The sterile ophthalmic product will be (b) (4) The sponsor should provide endotoxin specifications targeted at NMT (b) (4)

**Reviewing Microbiologist:** Vinayak B. Pawar, Ph.D.

**Date**

**Secondary Concurrence:** Bryan S. Riley, Ph.D.

**Date**

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/s/  
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VINAYAK B PAWAR  
03/23/2011

BRYAN S RILEY  
03/23/2011  
I concur.