CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202667Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202667 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: COSOP PF Established/Proper Name: Dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5% Dosage Form: ophthalmic solution		Applicant: Merck, Sharp & Dohme, Corp. Agent for Applicant (if applicable):
RPM: Alison Rodgers/Judit Milstein		Division: Transplant and Ophthalmology Products (DTOP)

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is March 24, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR: December 16, 2011

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

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❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5 (new formulation)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee ☐ Yes ☐ No

bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP: February 1, 2012 CR: December 16, 2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 24, 2012
• Original applicant-proposed labeling	February 16, 2011
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

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Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 24, 2012
• Original applicant-proposed labeling	February 16, 2011
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	January 24, 2012
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	January 30, 2012 (e-mail-no need to review tradename again) October 14, 2011 (pre-action review) May 16, 2011 (letter) May 13, 2011 (review)
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM March 21, 2011 ☒ DMEPA August 2, 2011 ☒ DMPP/PLT (DRISK) December 19, 2012 (consult) December 21, 2011(review) ☒ ODPD March 23, 2011-Consult: September 30, 2011(review) ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing: March 23, 2011 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

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EXCLUSIVITY SUMMARY

NDA # 202667 SUPPL # HFD # 590

Trade Name COSOPT PF

Generic Name dorzolamide hydrochloride-timolol maleate, ophthalmic solution, 2%/0/5%

Applicant Name Merck Sharp & Dohme, Corp.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES is this approval a result of the studies submitted in response to the Pediatric Written Request? YES ☐ NO ☒

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

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NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	20869-Cosopt PF	Dorzolamide hydrochloride/timolol maleate
NDA#	20408-Trusopt	Dorzolamide
NDA#	18086-Timoptic	Timolol maleate

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

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YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study P081: A Multiple-Dose, Double- Masked, Parallel, Active Treatment Controlled Study of Preservative-Free 2.0% Dorzolamide / 0.5% Timolol Combination and 2.0% Dorzolamide / 0.5% Timolol Combination with Preservative in Patients With Elevated IOP

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a

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similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study P081: A Multiple-Dose, Double- Masked, Parallel, Active Treatment Controlled Study of Preservative-Free 2.0% Dorzolamide / 0.5% Timolol Combination and 2.0% Dorzolamide / 0.5% Timolol Combination with Preservative in Patients With Elevated IOP

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 52080	YES ☒	! NO ☐
		! Explain:

Investigation #2	N/A	!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

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Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Rhea A. Lloyd, MD
Title: Medical Officer
Date: 01/30/2012

Name of Office/Division Director signing form: Renata Albrecht, MD
Title: Director
Date: January 31, 2012

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

JUDIT R MILSTEIN
01/31/2012

RENATA ALBRECHT
01/31/2012

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Chitkala Kalidas
Director
Worldwide Regulatory Group

31 Jan 2011
Date

Reference ID: 3084903

From: Townsend, Karen
Sent: Wednesday, January 25, 2012 11:51 AM
To: Milstein, Judit
Subject: RE: NDA 202667- COSOPT PF-Class 1 resubmission

Hi Judit,

This is close enough to the 90 day pre-action review that, DMEPA has indicated , it is still good to go and no further input from them is needed.

Thanks,
Karen

From: Milstein, Judit
Sent: Wednesday, January 25, 2012 10:21 AM
To: Townsend, Karen
Subject: RE: NDA 202667- COSOPT PF-Class 1 resubmission

Thanks
Judit

From: Townsend, Karen
Sent: Wednesday, January 25, 2012 10:21 AM
To: Milstein, Judit
Subject: RE: NDA 202667- COSOPT PF-Class 1 resubmission

Checking…they preaction review which was completed October 17,2011 may cover this ….will let you know…may not need a consult…will let you know!

From: Milstein, Judit
Sent: Wednesday, January 25, 2012 10:00 AM
To: Townsend, Karen
Subject: RE: NDA 202667- COSOPT PF-Class 1 resubmission

Do I need to issue a new consult?
Judit

From: Townsend, Karen
Sent: Wednesday, January 25, 2012 9:59 AM
To: Milstein, Judit
Subject: RE: NDA 202667- COSOPT PF-Class 1 resubmission

Yes, they will need to submit a TN request. The preaction review was completed in October 2011 and more than 90 days have passed since then.

From: Milstein, Judit
Sent: Wednesday, January 25, 2012 9:50 AM
To: Townsend, Karen
Subject: NDA 202667- COSOPT PF-Class 1 resubmission

Karen,
For NDA 202667- COSOPT PF, Merck, we issued a CR letter on December 16, 2011.
Yesterday, Merck They have made a complete response to our CR letter.
Do you need to review the proprietary name once more?

Thank you

Judit Milstein
Chief, Project Management Staff
DTOP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6170
Silver Spring, MD 20993
Phone: 301-796-0763
Fax: 301-796-9881

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

/s/

JUDIT R MILSTEIN
01/30/2012

14 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Reviewer's Comment:

1. *The established name on the carton and container labeling is not consistent with the package insert. Revise the established name throughout all labeling to read 'dorzolamide hydrochloride – timolol maleate ophthalmic solution) 2%/0.5%'*

2. *The placement of the ingredient strengths below the established name remains confusing and implies two different strengths of the drug product, COSOPT PF. The established name of the drug is '(dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%'. The percentage strengths should be placed on the same line as the rest of the established name.*

3. *Bold the statement "Throw away any unused single-use containers 15 days after first opening the pouch" in order to increase prominence.*

4. *The statements* (b) (4) *should be removed.*

1 page of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

(b) (4)

Reviewer's Comment:
On both the sample and trade container labels, the placement of the ingredient strengths below the established name remains confusing and implies two different strengths of the drug product, COSOPT PF. The established name of the drug is '(dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%'. The percentage strengths should be placed on the same line as the rest of the established name.

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/s/

ALISON K RODGERS
12/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Patient Labeling
Attn: Chris Wheeler/Carol McAlman

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Hyun Son, Division of Transplant and Ophthalmology Products, 301-796-1939

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 19, 2011		202667	Original application	February 16, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cosopt PF (dorzolamide hydrochloride and timolol maleate) ophthalmic solution	Standard PUDFA: 12/16/2011	Beta Blocker and carbonic anhydrase inhibitor	December 21, 2011

NAME OF FIRM: Merck Sharp and Dohme Corp

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Merck has submitted an original NDA on 2/16/2011. The PDUFA due date for this application is 12/16/2011. DTOP took a CR action on 12/16/2011 due to manufacturing issues. We do however have the SCPI and would like for patient labeling to review the patient package insert for this product. A reminder that this proposed product PPI is based upon your comments regarding Zioptan (tafluprost). I will send the word version of the SCIP and PPI in a separate email.
Thank you.

SIGNATURE OF REQUESTOR
Hyun Son, Pharm.D.

METHOD OF DELIVERY (Check one)
☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reference ID: 3060473

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/s/

HYUN J SON
12/19/2011

From: Rodgers, Alison
To: "Glassner, D. (Dori)"
Subject: RE: NDA 202667
Date: Tuesday, December 13, 2011 3:25:00 PM
Attachments: Cosopt PF DRAFT PI carton and container ONLY.doc

---

Hi Dori,

Please find attached our DRAFT label for Cosopt PF. We are happy to share our comments as of this date. We do not expect a response.

Unfortunately, the PPI has to be reviewed by other groups within the Agency and that process has not yet been completed.

Yes, I will send the action letter to you via email on Friday.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Tuesday, December 13, 2011 11:33 AM
To: Rodgers, Alison
Subject: NDA 202667

Alison,
Following our conversation last week regarding the status of the NDA, my manager spoke to Dr. Chambers. We understand the situation as Dr. Chambers explained it. When asked about any further labeling comments Dr. Chambers also explained that the Division had thought that they would "wrap" this up with the action on the application, but I was asked to contact you to see if it was possible to get any further labeling comments especially the PPI ahead of Friday's action date.

One last thing. Since in the past there has been some confusion with who to send FDA letters for this application to, I just wanted to make sure the action letter is e-mailed to me on Friday…thanks.

Regards,

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 52,080 **MEETING MINUTES**

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2C-50
Upper Gwynedd, PA 19454-2505

Dear Dr. Kalidas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for COSOPT (dorzolamide hydrochloride-timolol maleate ophthalmic solution).

We also refer to the telecon between representatives of your firm and the FDA on April 28, 2010. The purpose of the telecon was to discuss your development program for a preservative-free formulation of COSOPT.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 28, 2010, 12:00 – 1:00 PM
Meeting Location: Teleconference

Application Number: IND 52,080
Product Name: Cosopt Ophthalmic Solution
Indication: Elevated Intraocular Pressure
Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Wiley Chambers, M.D.
Meeting Recorder: Alison Rodgers

FDA ATTENDEES
Division of Anti-Infective and Ophthalmology Products
Wiley Chambers, MD, Acting Director
Jennifer Harris, MD, Medical Officer
Rima Izem, PhD, Statistical Reviewer
Lucious Lim, MD, Medical Officer
Rhea Lloyd, MD, Medical Officer
Martin Nevitt, MD, Medical Officer
Alison Rodgers, Project Manager
Yan Wang, PhD, Statistical Team Leader

SPONSOR ATTENDEES
Merck Sharp & Dohme Corp. (Merck)
Almira Chabi, MD, Associate Director, Clinical Research
Richard Entsuah, PhD, Executive Director, Biostatistics
Tamra Goodrow, PhD, Senior Director, Regulatory Affairs
David Hewitt, MD, Senior Director, Clinical Research
Tony Ho, MD, Section Head, Neurology, Clinical Research
Chitkala Kalidas, PhD, Director, Worldwide Regulatory Affairs
Rob Lupinacci, MS, Senior Biometrician, Biostatistics
Duane Snavely, MA, Director, Clinical Biostatistics
Gretchen Trout, US Regulatory Policy Lead

BACKGROUND

Merck submitted a request for a Pre-NDA Meeting on February 26, 2010, to discuss the development of a preservative-free formulation of Cosopt. A briefing package was submitted on March 25, 2010. The Division provided Merck with responses to the questions outlined in the

briefing package via email on April 26, 2010. The original questions and Agency Responses are restated below followed by meeting comments (as applicable).

The meeting served to clarify the Division's responses.

DISCUSSION

Clinical

Question 1
Merck believes that no additional clinical studies are required to support an NDA for the preservative-free formulation of 2% dorzolamide hydrochloride/ 0.5% timolol. Does the Agency concur?

Agency Response: *Protocol 081 together with cross reference to the studies submitted in support of Cosopt is sufficient to enable a review of a new drug application for the revised formulation of Cosopt. Equivalence between the two formulations is recommended to be defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over the three month period and being less than 1.0 mmHg for the majority of direct group comparisons; the time points should include both the peak and trough efficacy times for both the test and control agents. It is unclear from the protocol you submitted whether you used an adjusted ANCOVA analysis (adjusting for baseline characteristics and possible interaction effects) or whether you used an unadjusted analysis to derive the confidence intervals. Please present both the adjusted and unadjusted analyses. When the NDA is submitted, please present these analyses for the two endpoints change of IOP from baseline and raw IOP, at every visit (peak and trough).*

MEETING COMMENTS:

- The Division clarified that Merck could conduct their adjusted analysis as it was submitted in the background package, but they should also submit the unadjusted analysis.
- Merck inquired as to whether or not they could conduct an analysis of raw IOP with adjustment for the baseline IOP. The Division stated that additional analyses of raw IOP with and without adjustment for the baseline IOP should be conducted and submitted for review.

Question 2
Merck considers that this is an appropriate method to analyze the data. Does the Agency concur?

Agency Response: *Yes. As part of the sensitivity analyses, it is recommended that both an "Intent-to-Treat with the last observation carried forward for missing data" analysis and a "Per-Protocol using only observed data" analysis be submitted. The "Intent-to-Treat" analysis should include all randomized patients. The "Per-Protocol" analysis should exclude patients with any protocol deviations and should exclude any incomplete patient data from the analysis.*

MEETING COMMENTS:

- Merck noted that only 3 patients who were randomized did not receive study medication. The Division agreed that there are unlikely to be significant differences between an analysis of all treated patients and all randomized patients. Merck would not necessarily have to submit analyses of both patient populations.

Question 3
Merck believes that the presentation of safety and efficacy and the format of the CSR for Protocol 081 are acceptable to support the review of the NDA. Does the Agency concur?

Agency Response: *See responses to Question #1 and #2. In addition, the Agency expects the full datasets to be submitted along with copies of the source code used to perform the analyses.*

MEETING COMMENTS:

- The Division agreed that Merck could provide SAS transfer files for all of their efficacy and safety data. Merck agreed to provide raw data sets as SAS transfer files and to provide SAS programs for the primary and secondary efficacy and safety analyses.

Question 4
Therefore, no pooled efficacy or safety analyses will be provided in the CTD. Does the Agency concur with this approach?

Agency Response: *Yes.*

There were no additional comments.

Question 5
Does the Agency concur that the clinical data, as outlined in the Table of Contents for Modules 2.5 and 2.7, would be adequate to support review of the NDA for the preservative-free-formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate?

Agency Response: *See responses to Question #1 and #2. In addition, the Agency expects the full datasets to be submitted along with copies of the source code used to perform the analyses (see Question 11 below).*

There were no additional comments.

Question 6
Merck proposes to submit the integrated post marketing safety data for both the preservative-free and preservative-containing formulations of 2% dorzolamide hydrochloride/0.5% timolol maleate as part of Module 2.7 for the NDA for the preservative-free formulation.
Does the Agency concur with this approach?

Agency Response: *Yes. This integrated safety data will most likely be used for developing the labeling for the drug product.*

There were no additional comments.

Non-clinical

Question 7
Does the Agency agree that the three new pre-clinical pharmacodynamic studies in addition to the pre-clinical safety program that supported registration of COSOPT®, TRUSOPT® and TIMOPTIC® will be adequate to support the review of an NDA for the preservative-free formulation of 2% dorzolamide hydrochloride/0.5% timolol maleate?

Agency Response: *Yes.*

There were no additional comments.

Quality

Question 8
We believe that the proposed contents of the chemistry, manufacturing and controls section of the CTD, as outlined in the Table of Contents contained in Section 7 of this Background Package will be adequate to allow review of the NDA for the preservative-free formulation of 2% dorzolamide/0.5% timolol. Does the Agency concur?

Agency Response: *In addition to the proposed table of contents, please include updated information on the following:*
1) Drug substance specifications
2) Drug substance manufacturing and testing facilities
3) A summary of the CMC changes made in the drug substances of the referenced NDAs since approval.
The adequacy of the CMC content will be a review issue.

There were no additional comments.

Pediatric Population

Question 9
Merck would like to request a waiver from any additional studies in pediatric patients. Does the Agency concur?

Agency Response: *This submission of this application would not appear to trigger the Pediatric Research Equity Act (PREA), i.e. no new active ingredient, no new indication, no new dosage form, no new dosing regimen, or no new route of administration. A waiver is therefore not necessary.*

There were no additional comments.

Risk Evaluation and Mitigation Strategies (REMS)

Question 10
Merck proposes that routine pharmacovigilance measures (labeling and spontaneous adverse event reporting) are appropriate for the management of the product's risks and that no formal REMS is required. Does the Agency concur with Merck's proposal regarding the REMS plan?

Agency Response: *We have not identified an issue to date which would necessitate the need for a REMS, however we are not able to fully comment until the NDA has been submitted and reviewed.*

There were no additional comments.

Plans for Electronic Submission

Question 11
Does the Agency concur with our plans for submission of data?

Agency Response: *The Case Report Forms for all discontinued patients, regardless of the reason for their discontinuation, should also be submitted to the NDA.*
Please add a folder named 'datasets' in Module 5. This folder should include the following subfolders for each study:

1) *Raw datasets along with the defined document, blank and annotated CRFs*
2) *Derived datasets along with the defined document*
3) *SAS programs used to produce the derived datasets*
4) *SAS programs used to produce the summary tables, figures and listings for the study report*

We recommend that the format of the dataset be complied with the CDISC SDTM requirements.
Specific requests for derived data set QIOP you present in define.pdf file are:

- *Please add a flag variable indicating whether the subject's observation is in the per protocol analysis or not in the per protocol analysis.*

- *Please add a categorical variable coding the reason for exclusion from the per protocol analysis for subjects who are excluded.*

- *Specify whether the two variables RESPONS3 and RESPONS4 in this data represent the imputed or the raw IOP measurements. Please have both the raw IOP measurements (prior to any imputation, left (OS) and right (OD) eyes) and the imputed IOP measurements (using LOCF, left (OS) and right (OD) eyes) as four separate variables.*

Please clarify why the variable visit number 'VISITNUM' was not captured in this data set.

MEETING COMMENTS:

- Merck plans to submit items 1 and 2 as well as the SAS programs used to produce the derived datasets with the understanding that the programs were not based on the raw SAS transport files. The Division agreed.
- Merck explained that it would be difficult to follow the *CDISC SDTM* standard because the study was conducted a number of years ago and the database structure was built differently from the *CDISC SDTM* standard. The Division stated that it understood and requested that a define.pdf file be submitted which fully defined all variables.

Question 12

Although the NDA for preservative-free 2% dorzolamide/0.5% timolol is intended to be submitted in the eCTD format, Merck proposes to cross reference pre-clinical and clinical studies previously submitted to the FDA as part of NDAs for COSOPT®, TRUSOPT® and TIMOPTIC® that were in the non e-CTD paper format. Text reference/citation to the original NDA number, date of approval of NDA and the appropriate sections will be included in the relevant eCTD modules.
Does the Agency concur with this approach?

Agency Response: *Yes.*

There were no additional comments.

<u>Labeling</u>

Question 13
Assuming that the Agency finds the data in the NDA sufficient to support clinical equivalence between the preservative-containing and preservative-free formulations of 2% dorzolamide hydrochloride/0.5% timolol maleate, does the Agency agree with the proposed draft label language on Indication and Usage and Dosage and Administration?

Agency Response: *Labeling is a review issue, and we are not able to comment until the NDA has been submitted and reviewed. We note that the product does not appear to have been studied in a patient population who is sensitive to a preservative and it is unlikely that the indication as proposed would be acceptable.*

There were no additional comments.

Question 14
As COSOPT® is the registered trademark for the preservative-containing product previously approved by the FDA and the suffix PF will be used to differentiate the preservative-free formulation from the preservative-containing formulation, Merck believes that no additional trademark review would be required by the FDA. Does the Agency concur?

Agency Response: *No. The proposed tradename would require a formal submission by Merck and review by the Division of Medication Error Prevention and Analysis (DMEPA).*

There were no additional comments.

ISSUES REQUIRING FURTHER DISCUSSION

There are no items requiring further discussion.

ATTACHMENTS AND HANDOUTS

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-52080	GI-1	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	TIMOPTIC/TRUSOPT(DORZOLAMIDE HCL/TIMOLOL

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/s/

WILEY A CHAMBERS
05/13/2010

Dori
****

Dori L. Glassner
Director , Worldwide Regulatory Affairs
T: +1 732 594 2735
F: +1 732 594 1030
dori.glassner@merck.com
Merck and Co., Inc.
126 East Lincoln Avenue
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/s/

ALISON K RODGERS
12/19/2011

From: Rodgers, Alison
To: "Glassner, D. (Dori)";
Subject: RE: NDA 202667 Review status inquiry
Date: Wednesday, November 16, 2011 1:39:00 PM

Hi Dori,

I apologize for my delayed response. With regard to the PPI, the old format no longer exists. We must adhere to the formatting requirements listed in the regulations. The PPI has to be reviewed by other groups, but we expect that the final PPI for Cosopt PF will probably be similar to the PPI for Tafluprost.

I do not have any information regarding the comparability protocol except to say that as of this date, I have not been alerted of any issues.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

From: Glassner, D. (Dori) [mailto:dori.glassner@merck.com]
Sent: Wednesday, November 09, 2011 3:10 PM
To: Rodgers, Alison
Subject: NDA 202667 Review status inquiry

Hi Alison,
I wanted to touch base with you to see if you knew when we can expect any further feedback on our proposed changes to the labeling that we provided via e-mail on September 30 and October 19 . We are especially interested in knowing about the

PPI and if/when we can expect any comments. In our response on September 30 we had indicated that we strongly believed the PPI should be maintained. The draft Cosopt PF PPI was based on the approved PPI for Cosopt preservative containing with some content wise changes based on the formulation change and editorial changes based on comprehension testing results. These changes were highlighted in the annotated labeling that was included in the NDA.

Additionally, I would like to take the opportunity to see if you anticipate any last minute CMC comments or issues from either ONDQA or the review Division.

Finally, in August when I contacted you about the status of the comparability protocol, you had indicated the following:
Regarding the comparability protocol, at this time we do not anticipate any problems, but the acceptability of the comparability protocol is a review decision and will be decided when the review is finalized.
I was wondering if you had any updated information.

Regards,
Dori
****

Dori L. Glassner
Director , Worldwide Regulatory Affairs
T: +1 732 594 2735
F: +1 732 594 1030
dori.glassner@merck.com
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Office location RY32-217
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/s/

ALISON K RODGERS
11/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202514
NDA 202667

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Merck Sharp & Dohme Corp.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Applicant:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Product Name/Dosage Form
202514	Zioptan (tafluprost ophthalmic solution), 0.0015%
202667	Cosopt PF (dorzolamide hydrochloride and timolol maleate ophthalmic solution), 2%/0.5%

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-0833.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
09/29/2011

From:	Rodgers, Alison
To:	"Glassner, D. (Dori)"
Subject:	NDA 202667 - Cosopt PF - Draft Label
Date:	Wednesday, September 21, 2011 1:33:00 PM
Attachments:	Cosopt PF label 092111.doc

Hi Dori,

Attached please find our draft label for Cosopt PF. Please review and respond by September 30th if possible. We would be happy to discuss the label with you by tcon if that would be helpful.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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/s/

ALISON K RODGERS
12/30/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202667 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, Mail Drop RY33-204
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dorzolamide hydrochloride and timolol maleate ophthalmic solution.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request your written response submitted by September 23, 2011, in order to continue our evaluation of your NDA.

1. In your amendment dated May 27, 2011, you provide stability data for batches 230-114-1, 230-118-01, and 230-119-01 (Reference 0005 – MCSS Stability Data). On examining the data closely we find that the numbers for weight loss are identical for each batch although the other data show the random batch to batch variation that one might expect. Please provide an explanation of the interesting observation. Please also provide a description of the weight loss test method and copies of the raw data, e.g., laboratory notebooks, that show how the weight loss stability data were obtained for the batches in question.

2. Please describe the foil used for these batches and batches 0668540, 0668970, and 0669710 previously reported in the NDA. Do the foil overwraps differ in overall size or sealing area?

3. Please indicate the location where stability testing was performed for each stability lot referenced in the submission. If stability testing was performed in multiple locations, please indicate the association between each individual lot and the testing location.

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
09/09/2011

Rodgers, Alison

From: Glassner, D. (Dori) [dori.glassner@merck.com]
Sent: Thursday, July 28, 2011 10:10 AM
To: Rodgers, Alison
Subject: RE: NDA 202667 - Request for Clarification

Alison,
E-mail received. I have am aiming to provide an e-mail response to the query by August 2. I am waiting for confirmation from the appropriate people that I will have it by this date.

On another matter. We received some additional CMC queries dated July 20, but because they were sent by regular mail we did not actually get them until July 26 and the according to the letter a response was requested by July 29. I called the PM listed on the letter Althea Cuff and left a message explaining this and asking if we could submit a response by August 5 instead, but I have not heard back from her yet and wasn't sure what to do.
Is it possible for you to help out with this?
Dori

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Thursday, July 28, 2011 9:06 AM
To: Glassner, D. (Dori)
Subject: NDA 202667 - Request for Clarification

Hi Dori,

Could you please clarify if the Cosopt PF labels will be affixed directly to the LDPE containers or be attached to a piece that comes off of the container. We are trying to gain a better understanding of the placement of the label. We would appreciate it if you could clarify this issue schematically.

Please respond to this request by August 2nd if at all possible.

Please let me know if you have any questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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ALISON K RODGERS
07/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-667 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, PhD
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, Mail Drop RY33-204
Rahway,NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dorzolamide hydrochloride and timolol maleate ophthalmic solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 29, 2011 to continue our evaluation of your NDA.

1. Please provide the structure of [redacted] (b) (4) in the specification for dorzolamide drug substance.

2. The eye is a sensitive organ. Please change the "Any unspecified (degradant) at NMT [redacted] (b) (4)" to "Any unspecified impurity at NMT [redacted] (b) (4)". If the word degradant is preferred over impurity, a separate criterion at NMT [redacted] (b) (4) may be set for potential leachables

3. Please describe the composition of the [redacted] (b) (4) foil used to package the stability batches described in the original application and compare it to the foils proposed for use in the commercial product, i.e., [redacted] (b) (4)

4. Please commit to placing the first 3 commercial batches packaged using each of the foils proposed for the commercial product [redacted] (b) (4) on long-term stability with additional periodic monitoring for weight loss.

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
07/20/2011

Rodgers, Alison

From: Glassner, D. (Dori) [dori.glassner@merck.com]
Sent: Monday, June 27, 2011 5:40 PM
To: Rodgers, Alison
Subject: RE: NDA 202607 - Cosopt PF

confirming receipt

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Monday, June 27, 2011 4:08 PM
To: Glassner, D. (Dori)
Subject: NDA 202607 - Cosopt PF

Hi Dori,

In reference to your May 27, 2011, response to a CMC/Microbiology Information Request sent April 19, 2011, please note the following regarding endotoxin drug product specifications:

Endotoxin produces pyrogenic reactions even with topical ophthlamic application. It is unclear why you would want to include endotoxin in your drug product.

Endotoxin should be controlled in topical ophthlamic products. It is recommended that applicants include an endotoxin specification for topical ophthlamic products targeted at an acceptance level of (b) (4)

Please let me know when you plan to submit your response to the NDA.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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/s/

ALISON K RODGERS
06/29/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202667

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Merck Sharp & Dohme Corp.
126 E. Lincoln Avenue
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

ATTENTION: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated February 16, 2011, received February 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution, 2 %/0.5 %.

We also refer to your February 16, 2011, correspondence, received February 16, 2011, requesting review of your proposed proprietary name, Cosopt PF. We have completed our review of the proposed proprietary name, Cosopt PF and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 16, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alison Rodgers at (301) 796-0797.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/16/2011

Rodgers, Alison

From: Glassner, D. (Dori) [dori.glassner@merck.com]
Sent: Monday, April 25, 2011 7:24 PM
To: Rodgers, Alison
Subject: RE: NDA 202667 Preliminary Label Formatting Comments

Hi Alison,
I am confirming receipt of this e-mail as requested.
Dori

From: Rodgers, Alison [Alison.Rodgers@fda.hhs.gov]
Sent: Monday, April 25, 2011 3:03 PM
To: Glassner, D. (Dori)
Subject: NDA 202667 Preliminary Label Formatting Comments

Hi Dori,

During our preliminary review of your submitted labeling, we have identified the labeling format issues listed in the attached document.

We request that you resubmit labeling that addresses these issues by May 23, 2011. The resubmitted labeling will be used for further labeling discussions.

Please let me know if you have any questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective and Ophthalmology Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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1) Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

2) Must include the verbatim statement: **"See 17 for Patient Counseling Information"** or if the product has FDA-approved patient labeling: **"See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

3) The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

4) Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

5) For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

   "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

6) The subheading, Teratogenic effects, and the Pregnancy Category should be included under subsection 8.1 Pregnancy, not under subsection 13.1 Carcinogenesis, mutagenesis, impairment of fertility.

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/s/

ALISON K RODGERS
05/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202667

FILING COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, PhD
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, Mail Drop: RY33-204
Rahway, NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated February 16, 2011, received February 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dorzolamide hydrochloride and timolol maleate ophthalmic solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 16, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 18, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. None of these criteria apply to your application; therefore, you are exempt from this requirement.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Drug Evaluation Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
04/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-667 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, PhD
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, Mail Drop RY33-204
Rahway,NJ 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dorzolamide hydrochloride and timolol maleate ophthalmic solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please continue testing for particulate matter on stability.
2. Measure weight change on stability for at least one batch through the expiration dating period.
3. Test the drug product for endotoxins at release and on stability, at least annually.
4. Test at least one stability batch for leachables using appropriate screening methods.
5. In section P.8.2 you state "If any production batch does not conform to approved specifications, the results will be investigated immediately and appropriate action taken." In accordance with 21 CFR 314.81(b)(1), please commit to reporting any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification to the FDA and the review division within 3 working days.
6. In the Detailed Process Description (P.3.3.3, page 7) you state (b) (4) (b) (4) Provide actual numbers for this statement or otherwise describe how sterility is assured.
7. In the validation of the timolol HPLC method the linearity is given as 1 (P.5.3.2, page 10). Please express this value to 4 significant figures.
8. Provide data for the stability of the solutions used in the timolol HPLC method.
9. You report that intermediate precision is demonstrated for the dorzolamide HPLC method by using (b) (4) (P.5.3.1, page 15). You also imply that different equipment and columns are used (P.5.3.1, page 11). Clarify how intermediate precision is demonstrated for this method.

10. For P.5.5 Characterization of Impurities you state "Information on the characterization of impurities is provided previously in the drug substance section 3.2.S.3.2-0507 and 3.2.S.3.2-0950." We could not find this information in this application.
11. For P.6 Reference Standards or Materials you state "Information on the reference standards or reference materials are provided previously in the drug substance Reference Standards or Materials section, Sec. 3.2.S.5-0507 and 3.2.S.5-0950." We could not find this information in this application.
12. (b) (4) Please clarify. Also the (b) (4) (b) (4) appears to (b) (4) so presumably cannot be imprinted (P.7, page 5). Is this correct?

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAPTI D MADURAWE
04/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202667

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, PhD
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, Mail Drop RY33-204
Rahway,NJ 07065-0900

Dear Dr. Kalidas:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: dorzolamide hydrochloride and timolol maleate ophthalmic solution

Date of Application: February 16, 2011

Date of Receipt: February 16, 2011

Our Reference Number: NDA 202667

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 17, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Your proposal to submit the next Periodic Safety Update Report covering August 19, 2010, to February 18, 2011, in lieu of a 120-day Safety Update Report is **not** acceptable.
You are required to update the application with new safety information four months after the initial submission as per 21 CFR 314.50 (d)(5)(vi)(*b*).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was

amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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MAUREEN P DILLON PARKER
03/01/2011