

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**203168Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203168

SUPPL #

HFD #

Trade Name Prolensa

Generic Name bromfenac ophthalmic solution, 0.07%

Applicant Name Bausch & Lomb Incorporated

Approval Date, If Known : April 5, 2013

### 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:

d) Did the applicant request exclusivity?

YES  NO

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

3 Years

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?

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# 21664 Xibrom/Bromday

NDA# 20535 Duract

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#

NDA#

NDA#

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.

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:

- (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 -S00124-ER  
Study- S00124-WR

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

Investigation #2 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

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a 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-S00124-ER  
Study-S00124-WR

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 # 60295      YES       ! NO   
! Explain:

Investigation #2  
IND # 60295      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?

Investigation #1  
!  
! YES   
! NO   
! Explain:

Investigation #2  
!  
! YES   
! NO   
! 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: Michael Puglisi  
Title: Regulatory Project Manager  
Date: April 4, 2013

Name of Division Director signing form: Renata Albrecht, MD  
Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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.**  
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/s/  
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MICHAEL J PUGLISI  
04/05/2013

RENATA ALBRECHT  
04/05/2013



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**Debarment Certification for NDA 203168 for  
Bromfenac Ophthalmic Solution 0.07%**

ISTA Pharmaceuticals<sup>®</sup>, Inc. hereby certifies that it did not and will not use in any capacity the services of any person or entity debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed:

  
Marvin J. Garrett  
Vice President  
Regulatory Affairs, Quality Assurance  
& Compliance

09 FEB 2012  
Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 203168 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Prolensa Established/Proper Name: bromfenac sodium Dosage Form: ophthalmic solution		Applicant: Bausch & Lomb, Inc. Agent for Applicant (if applicable):
RPM: Michael Puglisi		Division: DTOP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 4/7/13</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

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

<sup>2</sup> 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., new listed drug, patent certification revised).

<p>of 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics<sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input checked="" type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> 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.

<p>Exclusivity</p>	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: 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.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>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.)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> 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)).</li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee 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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action and date: AP – 4/5/13
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included – Submitted 4/3/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included – Submitted 6/6/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Included – Submitted 3/18/13
<ul style="list-style-type: none"> <li>Proprietary Name                             <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	11/9/12  11/7/12, 3/4/13
<ul style="list-style-type: none"> <li>Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 8/20/13 <input checked="" type="checkbox"/> DMEPA 2/8/13 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 3/20/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	8/20/12
<ul style="list-style-type: none"> <li>All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>NDA only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>Pediatrics (<i>approvals only</i>)                             <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____                                      If PeRC review not necessary, explain: <u>Does not trigger PREA</u></li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)</li> </ul>	Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<b>Minutes of Meetings</b>	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 8/29/11
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/5/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/5/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See clinical review
• Clinical review(s) ( <i>indicate date for each review</i> )	3/22/13
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	In 3/22/13, Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management • REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	Included

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/4/13
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/4/13, 4/1/13
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 2/19/13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 7/23/12, 3/4/13
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/5/13
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 7/20/12, 7/26/12, 2/26/13, 4/4/13
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 1/22/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	In 2/26/13, Product Quality Review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 7/27/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

### Information Request

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**DATE:** March 4, 2013

<b>To:</b> B&L Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> E paul.nowacki@bausch.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Clinical/Stats Comments/Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find an information request from our clinical reviewer for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

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Information Request:

- 1) *A justification for the 3 mL in a 7.5 mL configuration is not provided in this application. A justification should be provided.*
- 2) *More subjects were evaluated for efficacy than were evaluated for safety in both S00124-ER and S00124-WR. This is not acceptable. Safety analyses were to be conducted on the Safety Population, defined as all randomized subjects who received at least 1 dose of IP. All analyses of efficacy were to be conducted on the Intent-to-Treat (ITT) Population, defined as all randomized subjects, where subjects were to be analyzed in the group to which they were randomized.*

*A reanalysis of the study data for S00124-ER and S00124-WR with the Safety Population defined consistent with the Intent-to-Treat (ITT) Population (i.e. all randomized subjects, where subjects were to be analyzed in the group to which they were randomized) should be submitted to the application.*

*This analysis should include, at least, the incidence of adverse events affecting the study eye: events with an incidence of  $\geq 2\%$  in the bromfenac 0.07% group or in the placebo group in both S00124-ER and S00124-WR, analyzed separately.*

- 3) *The definition of “study completion” as defined in Table 4 (Section 10.1 of the CSRs) for S00124-ER and S00124-WR is not acceptable. Subjects who discontinued investigational product early and completed the final study visit SHOULD NOT be considered to have completed the study. Revised tables for study disposition should be provided separately to the application for S00124-ER and for S00124-WR.*
- 4) *A table, similar to Table 14 (Section 11.4.1.2 of the CRs) for S00124-ER and S00124-WR, should be provided for each which summarizes the subjects N (%) with cleared cells at each visit, (LOCF, ITT Population).*

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/s/  
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MICHAEL J PUGLISI  
03/04/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

### Information Request

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**DATE:** February 6, 2013

<b>To:</b> B&L Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> E paul.nowacki@bausch.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Biostatistics Comments/Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find comments from our Biostats reviewer for NDA 203168. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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Information Request:

In our requested analysis, we wanted to treat the following two types of subjects as failures:

Type 1: Subjects who received a rescue therapy. We identified one such subject (subject 1603) in study S00124 WR.

Type 2: Subjects who had a SOIS score > 0 at Day 15 (regardless of whether they had a zero SOIS score at one of the visits prior to Day 15). We identified 15 such subjects as provided in the following table.

S00124-WR		S00124-ER	
Subject Id	Treatment Arm	Subject Id	Treatment Arm
0401	Placebo	5001	Placebo
0413	Placebo	5015	Placebo
1005	Placebo	6106	Placebo
1709	Placebo	7305	Placebo
0709	Bromfenac	6801	Bromfenac
1308	Bromfenac	6107	Bromfenac
2302	Bromfenac	7501	Bromfenac
2317	Bromfenac		

Our analysis results are provided below. Please let us know if you find any error in our analysis.

	Percentage of Subjects with Cleared Ocular Inflammation by Day 15*			
Study	Bromfenac 0.07%	Placebo	% Difference (95% CI)	P-value
S00124-ER	51/112 (45.5%)	14/108 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001
S00124-WR	50/110 (45.4%)	30/110 (27.3%)	18.1% (5.7%, 30.7%)	0.0076

\* Subjects who received a rescue therapy and subjects with a non-zero score at Day 15 (regardless of whether they had a zero score in prior visits) were set as failures; Missing data were imputed using LOCF

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/s/  
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MICHAEL J PUGLISI  
02/06/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

### Information Request

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**DATE:** January 25, 2013

<b>To:</b> B&L Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> E paul.nowacki@bausch.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Biostatistics Comments/Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find an information request from our Biostats reviewer for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

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Information Request:

For study S00124-ER and S00124-WR, please provide the analysis results for the primary efficacy endpoint by treating subjects who received a rescue therapy and subjects who didn't have cleared ocular inflammation at Day 15 (SOIS score>0) as failures.

Please present your results in a table similar to the mock-up table provided below.

	<b>Percentage of Subjects with Cleared Ocular Inflammation by Day 15</b>			
<b>Study</b>	<b>Bromfenac 0.07% N=112</b>	<b>Placebo N=108</b>	<b>% Difference (95% CI)</b>	<b>P-value</b>
<b>S00124-ER</b>	51(45.5%)	14 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001
<b>S00124-WR</b>	50 (45.4%)	30 (27.3%)	18.1% (5.7%, 30.7%)	0.0076

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/s/  
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MICHAEL J PUGLISI  
01/25/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

### Information Request

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**DATE:** November 26, 2012

<b>To:</b> Bausch & Lomb Pharmaceuticals	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> paul.nowacki@bausch.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** CMC Information Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find a CMC information request for NDA 203168. Please confirm you have received this request and let me know if you have any questions about anything. Thanks.

Mike

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Reviewer's Comments:

- 1) *In the NDA submission you provided 12 months of long-term, 6 months of accelerated stability data, and statistical plots of long-term stability studies and requested an expiration dating period of (b) (4) for the commercial drug product batches. We noticed that some lots had out of specification (OOS) results at the 6 months time point when stored under accelerated storage condition. Also you did not provide any intermediate term storage condition results. In order for us to evaluate the stability data completely, please provide the following information:*
  - a) *Stability data update covering more than 12 months of long-term condition study, as available to date.*
  - b) *Details of all statistical analyses of the long-term stability data.*
  - c) *A table showing the ranges of results observed for the tests that that were conducted on the stability lots at 25°C/40%RH and 40°C/20%RH. This information is needed for determining the acceptance criteria in the drug product specification.*
- 2) *Since OOS results for bromfenac assay, osmolality, and/or EDTA assay were observed at the 6 months time point when samples were stored at 40°C/20%RH for some of the primary stability batches, include 30°C/35% RH storage condition in the first three stability commitment batches.*
- 3) *The proposed 0.07% strength formulation is different from the approved 0.09% strength formulation. Therefore, discuss the fate of sodium sulfite during manufacture and storage of the drug product, including any impurities that could be formed due to interaction between the sodium sulfite and bromfenac and/or other excipients present in the proposed drug product.*
- 4) *The approved 0.09% strength drug product specification contains a test and acceptance criteria for sodium sulfite (NLT (b) (4) at release and NLT (b) (4) during stability) and a test for weight loss (in stability specification). Since some of the NDA stability batches of the proposed drug product showed OOS results for assay, osmolality, and/or EDTA content, inclusion of these tests and acceptance criteria in the commercial drug product specification will provide additional assurance regarding the purity, quality, safety, and efficacy of the drug product, therefore, please include the test and acceptance criteria for sodium sulfite in the commercial drug product release and stability specification and a test and acceptance criterion for weight loss in the stability specification.*
- 5) *Provide justification for the proposed holding period of the (b) (4) for up to (b) (4)*

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/s/  
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MICHAEL J PUGLISI  
11/26/2012



NDA 203168

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Bausch & Lomb Incorporated  
50 Technology Drive  
Irvine, CA 92618

Attention: Paul Nowacki  
Director, Regulatory Affairs

Dear Mr. Nowacki:

Please refer to your New Drug Application (NDA) dated June 6, 2012, received June 7, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Bromfenac Sodium Ophthalmic Solution, 0.07 %.

We also refer to your correspondence, dated and received August 31, 2012, requesting review of your proposed proprietary name, Prolensa. We have completed our review of Prolensa and have concluded that it is acceptable.

The proposed proprietary name, Prolensa, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 31, 2012 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 Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Puglisi at 301-796-0791.

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/  
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CAROL A HOLQUIST  
11/09/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

## Information Request

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**DATE:** November 7, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Quality Micro Information Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find a Quality Micro information request for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

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Reviewer's Comments:

Please address the following review issues:

1. Provide the raw data (plate counts) for the preservative effectiveness test results provided in tables J3-1, J3-2, and J3-3 located in the "Preservative Effectiveness Tests and Methods" document located in section 3.2.P.3.5 of the application.
2. Provide the following information regarding endotoxin testing for Prolensa<sup>TM</sup>
  - a. The endotoxin limit for the drug product (an endotoxin limit of (b) (4) is suggested)
  - b. The test method to be used for endotoxin testing
  - c. Calculation of the maximum valid dilution
  - d. The results of inhibition/enhancement testing
  - e. Inclusion of the endotoxin limit and test method in the list of drug product specifications.

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MICHAEL J PUGLISI  
11/08/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

## Information Request

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**DATE:** November 1, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Quality Micro Information Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find a Quality Micro information request for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

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Reviewer's Comment:

*A product quality microbiology review of NDA 203-168 is in progress. Please address the following issues:*

1. Provide a justification for

(b) (4)

[Redacted content]

2. Provide a copy of

(b) (4)

[Redacted content]

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MICHAEL J PUGLISI  
11/01/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

## Information Request

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**DATE:** August 21, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Biostatistics Comments/Request for NDA 203168

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**Total no. of pages including cover: 2**

**Comments:**

Hi Paul,

Attached please find comments from our Biostats reviewer for NDA 203168. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

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Reviewer's Comments:

Please provide an updated subject disposition table as shown on the mock table below for both studies and separately and for the combined analysis. Please also include a subject identification number in all data sets. For example we were not able to locate the SUBJID variable in the MEDS data set which contains the records of subjects who have used Rescue Medication. We need to merge different data sets to be able to replicate your results and conduct some additional analyses of our own.

**Table 4. Summary of Subject Disposition**

	<b>Bromfenac 0.07% n(%)</b>	<b>Placebo n(%)</b>	<b>P-value <sup>2</sup></b>
Number of Subjects Randomized	110 (100%)	110 (100%)	
Subjects who Completed the Study <sup>1</sup>	104 (94.5%)	100 (90.9%)	
Subjects discontinue IP prematurely	104 (94.5%)	100 (90.9%)	
Subjects who received any rescue therapy	104 (94.5%)	100 (90.9%)	
Subjects who received rescue therapy for pain and inflammation (Eye)	104 (94.5%)	100 (90.9%)	
Subjects who Discontinued the Study Early	6 (5.5%)	10 (9.1%)	0.3024
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	4 (3.6%)	3 (2.7%)	
Lost to Follow-up	0	0	
Death	0	0	
Other <sup>3</sup>	2 (1.8%)	7 (6.4%)	
Cancelled surgery			
Disallowed medication at enrollment			
Disallowed medication during study			
Experienced SAE			

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/s/  
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MICHAEL J PUGLISI  
08/21/2012



NDA 203168

**FILING COMMUNICATION**

ISTA Pharmaceuticals, Inc.  
Attention: Paul Nowacki  
Director, Regulatory Affairs  
50 Technology Drive  
Irvine, California 92618

Dear Mr. Nowacki:

Please refer to your New Drug Application (NDA) dated June 5, 2012, received June 7, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Prolensa (bromfenac ophthalmic solution) 0.07%.

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 is 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 April 7, 2013.

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 March 10, 2013.

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.

Please note that we await your responses to our July 31, 2012, request for additional CMC, labeling, and biostatistics information as follows:

CMC:

1. Please submit color mock-ups of the carton and container labels.

2. The drug product specification proposes a test for weight loss and sodium sulfite but does not provide for acceptance criterion. Please propose a suitable acceptance limit for this test.

Labeling:

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. White space must be present before each major heading in the Highlights (HL).
2. In the Word and pdf versions of the labeling, a horizontal line must separate the HL and Table of Contents (TOC).
3. In the Word and pdf versions, the product title in the HL must be bolded.
4. In the Word and pdf versions, the Initial U.S. Approval in the HL must be bolded.
5. All contraindications listed in the FPI must also be listed in the HL or must include the statement “None” if no contraindications are known.
6. In the Word and pdf versions, a horizontal line must separate the TOC from the Full Prescribing Information (FPI).
7. In the FPI, if no Contraindications are known, this section must state “None.”
8. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because adverse reactions are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

9. The terms “adverse events” and “adverse experiences” should be avoided in the Adverse Reactions section. The term “adverse reactions” should be used.
10. The “Rx Only” statement that appears at the end of the package insert should be deleted. This statement is only required for container and carton labels.
11. Please submit mock-ups for the carton and container labels for all four presentations: 0.6 mL sample size, 0.8 mL sample size, 1.6 mL trade size, and the 3 mL trade size.

Statistics:

1. We were not able to locate the program codes you used to generate the tables and listings for study S00124-ER and study S00124-WR and for the ISE and ISS reports. Please submit these program codes with a detailed documentation. These program codes will help us to reproduce and evaluate your results, and expedite our review of your NDA. For example, without access to your SAS program “t1402010504.sas”, which was indicated in the footnote for Table 14.2.1.5.4 on page 299 of your study report for study S00124-ER, we cannot evaluate your analysis results based on the multiple imputation approach.
2. Please conduct safety and efficacy analysis for gender, racial, and geriatric subgroups for study S00124-ER and study S00124-WR in the same manner as you did for ISE and ISS reports.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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. Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

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/  
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RENATA ALBRECHT  
08/20/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

### Information Request

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**DATE:** July 31, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** CMC, Statistics, and Labeling Comments/Request for NDA 203168

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**Total no. of pages including cover: 3**

**Comments:**

Hi Paul,

Attached please find comments from our CMC, Statistics, and Labeling reviewers for NDA 203168. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike

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Reviewer's Comments:

CMC:

1. Please submit color mock-ups of the carton and container labels.
2. The drug product specification proposes a test for weight loss and sodium sulfite but does not provide for acceptance criterion. Please propose a suitable acceptance limit for this test.

Labeling:

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. White space must be present before each major heading in the Highlights (HL).
2. In the Word and pdf versions of the labeling, a horizontal line must separate the HL and Table of Contents (TOC).
3. In the Word and pdf versions, the product title in the HL must be bolded.
4. In the Word and pdf versions, the Initial U.S. Approval in the HL must be bolded.
5. All contraindications listed in the FPI must also be listed in the HL or must include the statement "None" if no contraindications are known.
6. In the Word and pdf versions, a horizontal line must separate the TOC from the Full Prescribing Information (FPI).
7. In the FPI, if no Contraindications are known, this section must state "None."
8. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*"Because adverse reactions are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."*

9. The terms "adverse events" and "adverse experiences" should be avoided in the Adverse Reactions section. The term "adverse reactions" should be used.
10. The "Rx Only" statement that appears at the end of the package insert should be deleted. This statement is only required for container and carton labels.
11. Please submit mock-ups for the carton and container labels for all four presentations: 0.6 mL sample size, 0.8 mL sample size, 1.6 mL trade size, and the 3 mL trade size

We request that you resubmit labeling that addresses these issues within three weeks. The resubmitted labeling will be used for further labeling discussions.

Statistics:

1. We were not able to locate the program codes you used to generate the tables and listings for study S00124-ER and study S00124-WR and for the ISE and ISS

*reports. Please submit these program codes with a detailed documentation. These program codes will help us to reproduce and evaluate your results, and expedite our review of your NDA. For example, without access to your SAS program “t1402010504.sas”, which was indicated in the footnote for Table 14.2.1.5.4 on page 299 of your study report for study S00124-ER, we cannot evaluate your analysis results based on the multiple imputation approach.*

- 2. Please conduct safety and efficacy analysis for gender, racial, and geriatric subgroups for study S00124-ER and study S00124-WR in the same manner as you did for ISE and ISS reports.*

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/s/  
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MICHAEL J PUGLISI  
07/31/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

## Information Request

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**DATE:** July 13, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Quality Micro Information Request for NDA 203168

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**Total no. of pages including cover: 1**

**Comments:**

Hi Paul,

Below please find a Quality Micro information request for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

*Reviewer's Comment:*

*Please provide the results of bacteriostasis/fungistasis testing conducted to verify the USP sterility test for Prolensa.*

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MICHAEL J PUGLISI  
07/13/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products  
Division of Transplant and Ophthalmology  
Products**

## Information Request

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**DATE:** July 10, 2012

<b>To:</b> ISTA Pharmaceuticals, Inc.	<b>From:</b> Michael Puglisi, Regulatory Project Manager
<b>Attention:</b> Paul Nowacki	<b>e-mail:</b> Michael.puglisi@fda.hhs.gov
<b>e-mail:</b> pnowacki@istavision.com	<b>Phone Number:</b> 301-796-0791
<b>Phone Number:</b> 949-789-3109	

**Subject:** Clinical Information Request for NDA 203168

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**Total no. of pages including cover: 1**

**Comments:**

Hi Paul,

Below please find a clinical information request for NDA 203168. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

*Reviewer's Comment:*

*Please provide tables, similar to Tables 16.1.4.1, which include the site number, investigator, investigator address, and number of subjects enrolled at each site for S00124-ER and for S00124-WR. Please provide these revised tables by July 20, 2012.*

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/s/  
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MICHAEL J PUGLISI  
07/10/2012



NDA 203168

**NDA ACKNOWLEDGMENT**

ISTA Pharmaceuticals, Inc.  
Attention: Paul Nowacki  
Director, Regulatory Affairs  
50 Technology Drive  
Irvine, California 92618

Dear Mr. Nowacki:

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: Prolensa (bromfenac ophthalmic solution) 0.07%

Date of Application: June 5, 2012

Date of Receipt: June 7, 2012

Our Reference Number: NDA 203168

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 August 6, 2012, 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.

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 Transplant and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0791.

Sincerely,

*{See appended electronic signature page}*

Michael Puglisi  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL J PUGLISI  
06/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

MEETING MINUTES

IND 60295

ISTA Pharmaceuticals, Inc.  
Attn: Paul Nowacki  
Director, Regulatory Affairs  
50 Technology Drive  
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on August 29, 2011. The purpose of the meeting was to discuss the NDA filing of Bromfenac Ophthalmic Solution, 0.07% for treatment of ocular inflammation and pain associated with cataract surgery.

The official minutes of that meeting of teleconference is enclosed for your information. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:

6 Pages have been Withheld as a Duplicate Copy of the Memorandum of Meeting Minutes dated December 11, 2011 which is Located in the Chemistry Review Section of this NDA Approval Package.

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/s/  
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RAPHAEL R RODRIGUEZ  
12/11/2011

WILEY A CHAMBERS  
12/13/2011