

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207795Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 207795	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vyzulta Established/Proper Name: latanoprostene bunod Dosage Form: ophthalmic solution		Applicant: Bausch & Lomb Inc. Agent for Applicant (if applicable): N/A
RPM: Lois Almoza		Division: Division of Transplant and Ophthalmology Products
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) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:
<p>Note: 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.</p>		
<p>➤ Actions</p>		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 2/17/18 		<input checked="" type="checkbox"/> AP 11/2/17 <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		CR – 8/17/17 and 7/21/16
❖ 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 N/A		<input type="checkbox"/> Received N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

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.

Review priority: **Standard** Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:** MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ 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

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Actions and dates AP – 11/2/17, CR – 8/17/17 and 7/21/16
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ 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>	<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
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Acceptability letters dated 6/14/17 and 1/15/16; Non- acceptability letter dated 10/19/15
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i> 6/13/17, 1/13/16, and 10/16/15	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 8/27/15 DMEPA: <input checked="" type="checkbox"/> 5/25/17, 6/2/16 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 4/21/16 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input checked="" type="checkbox"/> ADL Review 8/3/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Filing Review completed September 17, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC December 2, 2015 If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> Type A mtg 9/22/17, 9/1/16
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	February 9, 2015
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	September 26, 2012
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	December 14, 2015
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	April 8, 2016
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	8/7/17, 7/21/16
Division Director Summary Review (<i>indicate date for each review</i>)	8/1/17, 6/17/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	8/1/17, 6/17/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	8/1/17, 4/21/16
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<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 (indicate date of review/memo)	Financial Disclosure Review begins on Page 63 of 4/21/16 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	8/1/17 4/1/16
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	OSI letters to investigators regarding site inspections dated 3/16/16 to Dr. David L. Wirta and Dr. William C. Christie dated 4/21/16.
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	4/22/16
Clinical Pharmacology <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"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	4/7/16
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	5/23/16
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	8/1/17, 5/20/16
❖ 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)	Page 108 of 5/20/16 Pharm/tox review
❖ 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
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	<input checked="" type="checkbox"/> No Separate Review
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	Quality Assessment 7/31/17, Drug Product Review 7/5/17, Drug Substance DMF Review 6/20/17, Drug Substance Review 6/15/17, Process Review 5/26/17 Quality Assessment 4/14/16 and 3/25/16, Methods Validation Report 11/25/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	Product Quality Microbiology Review dated 3/30/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Page 104 of 6/21/16 Review
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities

<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> NA <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	
<ul style="list-style-type: none"> ❖ Take Action Package (if in paper) down to Document Room for scanning within two business days 	



NDA 207795

MEETING MINUTES

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%. We also refer to the teleconference between representatives of your firm and the FDA on September 22, 2017. The purpose of the meeting was to discuss the Complete Response letter dated August 7, 2017.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Other

Meeting Date and Time: September 22, 2017 from 1:00PM – 2:00PM (EST)
Meeting Location: Teleconference

Application Number: 207795
Product Name: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
Indication: reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension

Applicant Name: Bausch & Lomb Inc.

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

John Farley, M.D., M.P.H.	Deputy Office Director, Office of Antimicrobial Products (OAP)
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Rhea Lloyd, M.D.	Clinical Reviewer, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Chunchun Zhang, Ph.D.	Acting Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Om Anand, Ph.D.	BioPharmaceutics Reviewer, OPQ/ONDP
Daniel Schu, Ph.D.	Product Quality Micro Reviewer, OPS/ONDQA
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/Division of Biometrics IV (DBIV)
Roy Blay, Ph.D.	Reviewer, Office of Scientific Investigations
Mahesh Ramanadham, Ph.D.	Director of Regulatory, OPQ/OPF/DIA
LCDR John W. Diehl, M.S.	Acting Director, Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations, Division II/Compliance Branch
Diana Willard	Chief, Project Management Staff, DTOP
Derek Alberding, Pharm.D.	Regulatory Health Project Manager, DTOP
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Tage Ramakrishna, M.D.	Chief Medical Officer and President, Research and Development/Quality
Louis Yu, Ph.D.	Chief Quality Officer
Dennis Asharin	Senior Vice President, Manufacturing
Angelo Conti	Vice President, Manufacturing
Sharon Tonetta, Ph.D.	Vice President, Regulatory Affairs
Ramesh Sedhain	Director, Quality (Bausch & Lomb Site)
E. Kwame Obeng, Ph.D.	Executive Director, Regulatory Affairs-CMC
J. Robert Hernandez	Director, Pharmaceutical Operations
Mary Harrell	Director, Regulatory Affairs-Product Lead
Isabelle Lefebvre, MSc	Vice President Regulatory Affairs, Branded & Generic Prescription Drugs, Consumer Products

BACKGROUND

An August 25, 2017, submission, from Bausch & Lomb Inc. (B&L) requested a meeting for NDA 207795 with the Agency regarding the Complete Response letter dated August 7, 2017. A Meeting Request Granted letter issued on, September 1, 2017. The August 25, 2017, Meeting Package was received August 25, 2016. Meeting Preliminary Comments were sent to B&L, via e-mail on, September 18, 2017. B&L forwarded talking points via e-mail on, September 20, 2017, and a request to change the format of the meeting to a teleconference.

DISCUSSION

Following, in **bold font**, are the questions in the August 25, 2017, Meeting Package. The FDA responses to these questions are in *italic* font. Talking points from the Sponsor sent via e-mail on, September 20, 2017, are in ***bold italic*** font. Discussions that took place during the September 22, 2017, teleconference are in regular font.

QUALITY QUESTIONS

Reference is made to the **Complete Response Letter** dated August 7, 2017, and the issues raised by the Agency regarding the recent inspection of the Bausch & Lomb Incorporated (Bausch & Lomb) manufacturing facility named in NDA 207795.

The initial response and updates provided through July 2017, are presented in **Attachment 2** of the Background Materials document.

1. Does the Agency agree that the response and updates provided to date satisfactorily resolve the inspection deficiencies associated with the Complete Response and resubmission of the above referenced application?

FDA Response:

To resolve the deficiency listed in the Complete Response action letter, the facility must be in compliance with current Good Manufacturing Procedures (cGMPs). In order for us to complete the facility assessment for NDA 207795 and make a determination that the facility is now in compliance with cGMPs, the Agency has the following information requests:

a. Regarding your response to Observation #1:

i.

(b) (4)

Bausch & Lomb Response:

As communicated previously in our 483 response and updates,

(b) (4)

(b) (4)

(b) (4)

Meeting Discussion: None

ii.

(b) (4)

Bausch & Lomb Response:

(b) (4)

Meeting Discussion: None

b. *Regarding your response to Observation #6:*

i.

(b) (4)

Bausch & Lomb Response:

As indicated in our 483 response and updates,

(b) (4)

(b) (4)

As mentioned in our 483 response updates,

(b) (4)

(b) (4)

Meeting Discussion: None

ii. *Provide non-conformance (b) (4) and work order (b) (4) (reference included in attachment #9 of July response) related to (b) (4) to support your firm's conclusions.*

Bausch & Lomb Response:

(b) (4)

(b) (4)

Attachments:

Attachment 01A, (b) (4) *and all associated attachments.*

Attachment 01B, (b) (4) *and all associated attachments.*

Attachment 01C, (b) (4)
(b) (4), *Enacted June 9, 2017 and all associated attachments.*

Meeting Discussion: None

iii. *Your June response indicates that* (b) (4) (b) (4)

Bausch & Lomb Response:

(b) (4)

Meeting Discussion: None

iv. *Provide an explanation of* (b) (4) (b) (4)
(b) (4) *as referenced in WC* (b) (4) *(Attachment #9 July Response).*

Bausch & Lomb Response:

(b) (4)

Attachments:

Attachment 02A, (b) (4)

Attachment 02B, (b) (4) *(See Attachment 01C)*

Meeting Discussion: None

c. Regarding your response to Observation#10

i. (b) (4)

Bausch & Lomb Response:

(b) (4)

Please direct your response to LCDR John W. Diehl, Acting Director of Compliance Branch, Office of Regulatory Affairs at john.diehl@fda.hhs.gov with a copy of the correspondence submitted to the NDA.

Meeting Discussion: The Applicant asked the status of cGMP compliance for their Tampa, Florida facility. The Agency stated that the cGMP compliance assessment was still under review. There were no additional questions that needed to be addressed at this time in order to finalize the facility assessment review.

The Agency noted that one of the facility reviewers is currently in San Juan, Puerto Rico, and the Agency expected to be speaking to him soon. The Applicant was told that if the Agency is unable to get in contact with staff in San Juan, Puerto then the Agency would work with other staff in order to complete the facility review.

The Applicant asked if all 483 deficiencies need to be completed for approvability. The Agency clarified that only the 483 deficiencies specifically relevant to the Vyzulta drug product are necessary for approvability of Vyzulta.

- 2. Will a manufacturing plant cGMP re-inspection, which would include a PAI of the Bausch & Lomb Tampa facility for NDA 207795, be required to close out the inspection deficiencies and for the regulatory hold (b) (4) to be lifted? If so, would the Agency please confirm timing of the necessary actions associated with closing any inspection related reviews?**

FDA Response:

In general, corrective actions implemented by your firm to address previous inspection deficiencies would need to be verified during the next inspection at the firm.

The facility assessment for this application is ongoing and therefore we cannot comment on the potential for a pre-approval inspection of the facility during this review cycle. A sufficient response to the information requested in our reply to question 1 above will facilitate our completion of the assessment. The need for a pre-approval inspection will be made following the completion of this assessment.

Bausch & Lomb Response:

Acknowledged with no further comment

Meeting Discussion: None

- 3. To confirm alignment with the Agency, if a re-inspection is required, would the Review Division, the Office of Pharmaceutical Quality and the District Office identify which action items require completion before the inspection deficiencies can be closed out?**

FDA Response:

Please see responses to Questions 1 and 2. If additional information is needed after you respond to the items listed above, we will notify you.

Bausch & Lomb Response:
Acknowledged with no further comment

Meeting Discussion: None

REGULATORY QUESTIONS

Reference is made to the Complete Response Letter dated August 7, 2017 (**Attachment 1** of the Background Materials document), and initial response and updates provided in response to the FDA Form 483 issued to Bausch & Lomb's Tampa, Florida facility on May 26, 2017 (**Attachment 2** of the Background Materials document). Additionally, reference is made to the resubmission of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution, 0.024%), dated August 17, 2017 (Sequence 0034) and the Resubmission acknowledgement letter dated August 23, 2017 (**Attachment 3** of the Background Materials document). A summary of the Regulatory supporting information is provided in **Section 1.6.2.10.2** of the Background Materials document under Regulatory.

4. When the cGMP deficiencies noted in FDA Form 483 issued on February 25, 2016 and May 26, 2017 are found to be satisfactorily addressed and remediated, will the Agency consider the approvability issue regarding NDA 207795 to be resolved?

FDA Response:

Yes.

Bausch & Lomb Response:
Acknowledged with no further comment

Meeting Discussion: None

5. Please confirm that all disciplinary review concerns, other than the Office of Pharmaceutical Quality, are complete and there are no further requests, other than labeling negotiation, required to achieve approval?

FDA Response:

Except as described in our reply to Questions 1 and 2, we have no further requests at this time.

Bausch & Lomb Response:
Acknowledged with no further comment

Meeting Discussion: None

Attachment - September 20, 2017, e-mail from Sponsor containing their responses to Agency Preliminary Comments

1.6.3 Correspondence Regarding a Meeting

1.6.3.1 Type A (Complete Response Letter) Sponsor's Meeting Minutes

1.6.3.2 Date, Time and Location of the Meeting

Date: September 22, 2017
 Time: 1:00 pm – 2:00 pm
 Location: 10903 New Hampshire Avenue
 White Oak, Building 22, Conference Room: 1315
 Silver Spring, Maryland 20903

1.6.3.3 Purpose of the Meeting

The purpose of the meeting is to have a discussion with the Agency regarding the Complete Response Letter (CRL) dated August 7, 2017 and Resubmission of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution, 0.024%) submitted to the Agency on August 17, 2017. Specifically, the Applicant seeks agreement with the Agency that the responses to the deficiencies noted in the CRL regarding the Tampa, Florida manufacturing facility have been adequately addressed to date and adequate information is available for review of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution, 0.024%) to obtain reasonable assurance of approvability.

The following identifies the application, drug, sponsor and proposed indication relative to the discussion.

- **Application:** NDA 207795
- **Drug:** Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
- **Sponsor:** Bausch & Lomb, Incorporated
- **Proposed Indication:** Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

1.6.3.3.1 Bausch & Lomb List of Attendees

Tage Ramakrishna, MD	Chief Medical Officer and President, Research and Development/Quality
Louis Yu, Ph.D	Chief Quality Officer
Dennis Asharin	Senior Vice President, Manufacturing
Angelo Conti	Vice President, Manufacturing
Sharon Tonetta, Ph.D	Vice President, Regulatory Affairs

Isabelle Lefebvre, MSc	Vice President Regulatory Affairs, Branded & Generic Prescription Drugs, Consumer Products
E. Kwame Obeng, Ph.D	Vice President, Regulatory Affairs-CMC
Ramesh Sedhain	Director, Quality (Bausch & Lomb Site)
J. Robert Hernandez	Director, Pharmaceutical Operations
Mary Harrell	Director, Regulatory Affairs-Product Lead

1.6.3.3.2 Food and Drug Administration List of Attendees

John Farley, M.D., M.P.H.	Deputy Office Director, Office of Antimicrobial Products (OAP)
Sunita Shukla, M.P.H., Ph.D.	Associate Director for Regulatory Science, (OAP)
Renata Albright, MD	Director, Division of Transplant and Ophthalmology Products
Wiley Chambers, MD	Deputy Director, Division of Transplant and Ophthalmology Products
William Boyd, MD	Cross Discipline Team Leader (CDTL), DTOP
Jennifer Harris, MD	Clinical Reviewer, Division of Transplant and Ophthalmology Products
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Derek Smith, Ph.D.	Acting Branch Chief, Office of Pharmaceutical Quality (OPQ)/ Office of Process and Facilities (OPF)/Division of Inspectional Assessment (DIA)
Chunchun Zhang, Ph.D.	Acting Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Mahesh Ramanadham, Pharm.D.	Division of Inspectional Assessment
John Diehl	FDA Office Representative for 483 Response
Milva Melendez, Ph.D.	Consumer Safety Officer, OPQ/Office of Surveillance (OS)
Teddi Lopez, Ph.D.	Supervisory Consumer Safety Officer, OPQ/OS

Lois Almoza, M.S

RPM, Division of Transplant and
Ophthalmology Products

1.6.3.4 List of Preliminary Questions and Comments

The following B&L questions from the Meeting Package dated August 25, 2017 are in **bold font**. The FDA responses to these questions are in *italic* font.

1.6.3.4.1 Quality Questions

Reference is made to the Complete Response Letter dated August 7, 2017, and the issues raised by the Agency regarding the recent inspection of the Bausch & Lomb Incorporated (Bausch & Lomb) manufacturing facility named in NDA 207795.

The initial response and updates provided through July 2017 are presented in Attachment 2 of the Background Materials document.

Question 1:

Does the Agency agree that the response and updates provided to date satisfactorily resolve the inspection deficiencies associated with the Complete Response and resubmission of the above referenced application?

FDA Comment:

To resolve the deficiency listed in the Complete Response action letter, the facility must be in compliance with current Good Manufacturing Procedures (cGMPs). In order for us to complete the facility assessment for NDA 207795 and make a determination that the facility is now in compliance with cGMPs, the Agency has the following information requests:

a. Regarding your response to Observation #1:

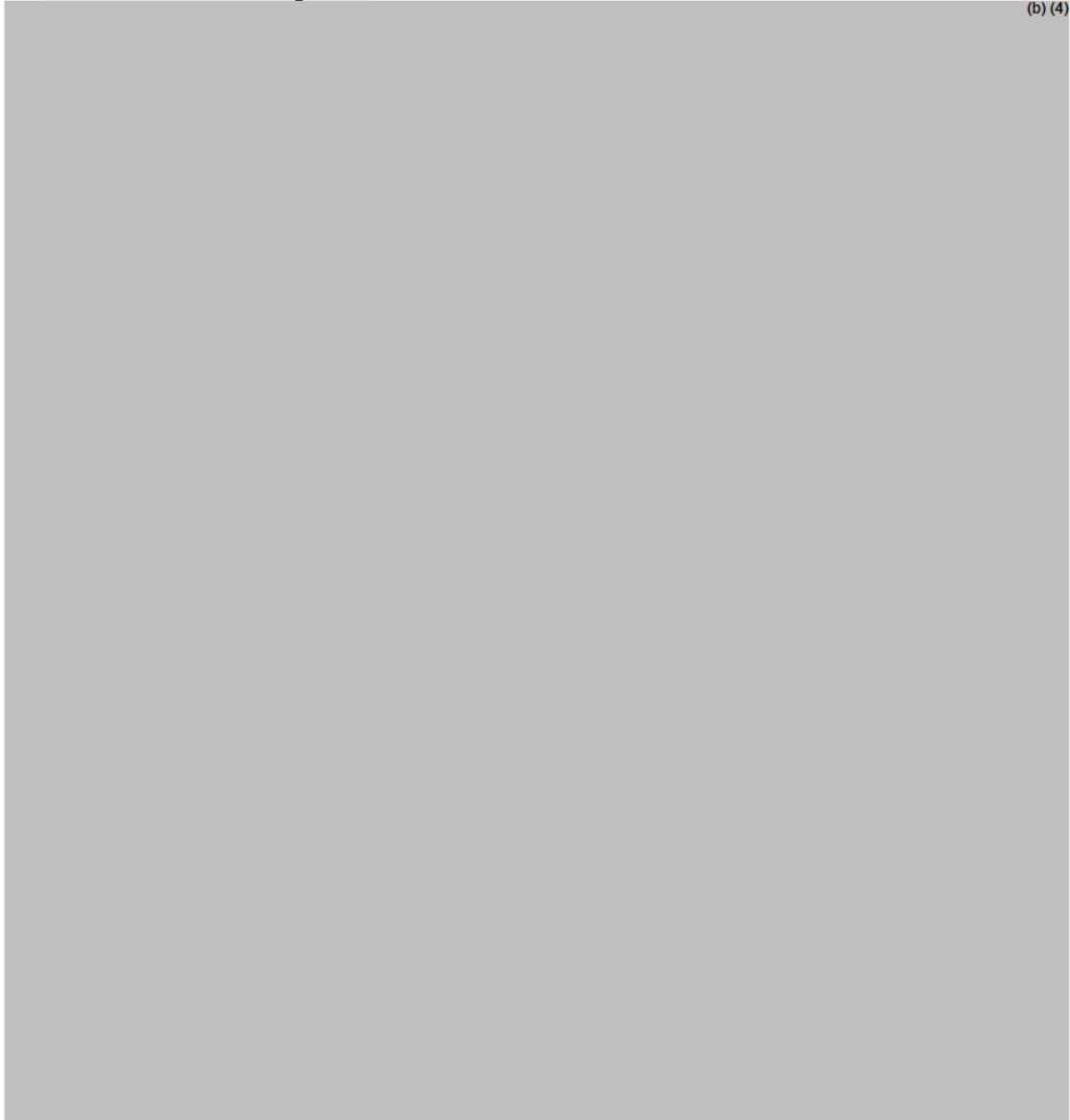
i. [Redacted] (b) (4)
[Redacted] (b) (4)

Bausch & Lomb Response:

As communicated previously in our 483 response and updates, [Redacted] (b) (4)
[Redacted] (b) (4)

Bausch & Lomb Response:

(b) (4)

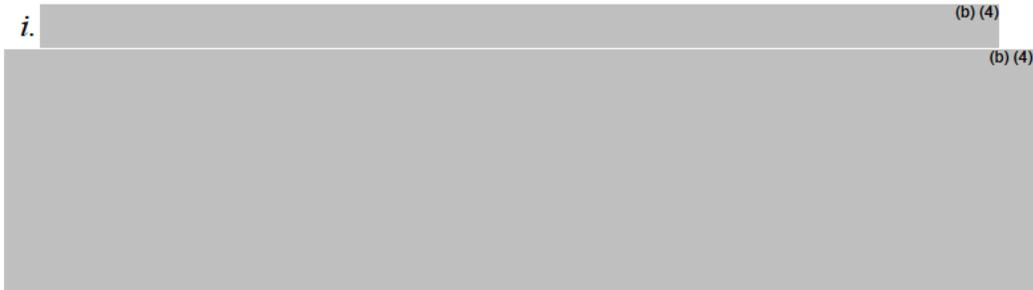


b. Regarding your response to Observation #6:

i.

(b) (4)

(b) (4)

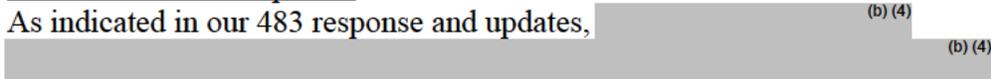


Bausch & Lomb Response:

As indicated in our 483 response and updates,

(b) (4)

(b) (4)



(b) (4)



As mentioned in our 483 response updates,

(b) (4)
(b) (4)



ii. Provide non-conformance (b) (4) and work order (b) (4) (reference included in attachment #9 of July response) related to (b) (4) to support your firm's conclusions.

Bausch & Lomb Response:

(b) (4)



Attachments:

Attachment 01A, (b) (4) and all associated attachments.

Attachment 01B, (b) (4) and all associated attachments.

Attachment 01C, (b) (4)
(b) (4), Enacted
June 9, 2017 and all associated attachments.

iii. Your June response indicates that (b) (4)
(b) (4) (b) (4)

Bausch & Lomb Response: (b) (4)

iv. Provide an explanation of (b) (4)
(b) (4) as referenced in WC (b) (4) (Attachment #9 July
Response).

Bausch & Lomb Response: (b) (4)

(b) (4)

Attachments:

Attachment 02A, (b) (4)

Attachment 02B, (b) (4)

&

c. Regarding your response to Observation#10

i. (b) (4)

(b) (4)

Bausch & Lomb Response:

(b) (4)

Please direct your response to LCDR John W. Diehl, Acting Director of Compliance Branch, Office of Regulatory Affairs at john.diehl@fda.hhs.gov with a copy of the correspondence submitted to the NDA.

Question 2:

Will a manufacturing plant cGMP re-inspection, which would include a PAI of the Bausch & Lomb Tampa facility for NDA 207795, be required to close out the inspection deficiencies and for the regulatory hold (b) (4) to be lifted? If so, would the Agency please confirm timing of the necessary actions associated with closing any inspection related reviews?

FDA Comment:

In general, corrective actions implemented by your firm to address previous inspection deficiencies would need to be verified during the next inspection at the firm.

The facility assessment for this application is ongoing and therefore we cannot comment on the potential for a pre-approval inspection of the facility during this review cycle. A sufficient response to the information requested in our reply to question 1 above will facilitate our completion of the assessment. The need for a pre-approval inspection will be made following the completion of this assessment.

Bausch & Lomb Response:

Acknowledged with no further comment

Question 3:

To confirm alignment with the Agency, if a re-inspection is required, would the Review Division, the Office of Pharmaceutical Quality and the District Office identify which action items require completion before the inspection deficiencies can be closed out?

FDA Comment:

Please see responses to Questions 1 and 2. If additional information is needed after you respond to the items listed above, we will notify you.

Bausch & Lomb Response:

Acknowledged with no further comment

1.6.3.4.2 Regulatory Questions

Reference is made to the Complete Response Letter dated August 7, 2017 (Attachment 1 of the Background Materials document), and initial response and updates provided in response to the FDA Form 483 issued to Bausch & Lomb's Tampa, Florida facility on May 26, 2017 (Attachment 2 of the Background Materials document). Additionally, reference is made to the resubmission of NDA 207795 for Vyzulta (latanoprostene bunod op hthalmic solution, 0.024%), dated August 17, 2017 (Sequence 0034) and the Resubmission acknowledgement letter dated August 23, 2017 (Attachment 3 of the Background Materials document). A summary of the Regulatory supporting information is provided in Section 1.6.2.10.2 of the Background Materials document under Regulatory.

Question 4:

When the cGMP deficiencies noted in FDA Form 483 issued on February 25, 2016 and May 26, 2017 are found to be satisfactorily addressed and remediated, will the Agency consider the approvability issue regarding NDA 207795 to be resolved?

FDA Comment:

Yes.

Bausch & Lomb Response:

Acknowledged with no further comment

Question 5:

Please confirm that all disciplinary review concerns, other than the Office of Pharmaceutical Quality, are complete and there are no further requests, other than labeling negotiation, required to achieve approval?

FDA Comment:

Except as described in our reply to Questions 1 and 2, we have no further requests at this time.

Bausch & Lomb Response:

Acknowledged with no further comment

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/s/

WILEY A CHAMBERS
10/19/2017

From: Almoza, Lois
Sent: Friday, August 11, 2017 12:08 PM
To: Harrell, Mary E (Mary.Harrell@bausch.com)
Subject: Labeling Discussion - NDA 207795/Vyzulta
(latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc.

Good Afternoon,

Please see the call-in information below for the 1:30pm teleconference today to discuss labeling only. Pay special attention to the Section 14, Clinical Studies.

Call-in # 1-855-828-1770

Meeting ID: (b) (4)

Thanks,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS A ALMOZA
08/11/2017

From: Almoza, Lois
Sent: Friday, June 23, 2017 9:43 AM
To: 'Harrell, Mary E'
Subject: Draft Label - NDA 207795/Vyzulta
(latanoprostene bunod ophthalmic solution), 0.024%/
Bausch & Lomb Inc.

Hi Mary,

Please see the attached draft package insert and
carton/container.

Thank you,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

LOIS A ALMOZA
06/23/2017



NDA 207795

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bausch & Lomb Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Mary Harrell, BsBM, RAC
Director, Regulatory Affairs

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated and received February 24, 2017, resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latanoprostene Bunod Ophthalmic Solution, 0.024%.

We also refer to your correspondence, dated and received March 17, 2017, requesting review of your proposed proprietary name, Vyzulta.

We have completed our review of the proposed proprietary name, Vyzulta and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 17, 2017 submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Lois Almoza, Regulatory Project Manager in the Office of New Drugs, at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/14/2017

From: Leahy, Kristine
To: "mary.harrell@bausch.com"
Cc: [Almoza, Lois](#)
Subject: FDA CMC Information Request NDA 207795- Please respond by COB--20-17
Date: Friday, April 07, 2017 1:18:00 PM
Attachments: [image001.png](#)
Importance: High

Dear Ms. Harrell,

Reference is made to the resubmission of the original new drug application (NDA 207795) submitted on February 24, 2017, for VYZULTA (latanoprostene bunod ophthalmic solution) 0.024%.

Our CMC Review team has the following comments/request:

Provide a summary table showing a side-by-side comparison of the manufacturing process, controls and equipment used in the manufacture of previous registration lots and new lots presented in the resubmission of 2/24/17. Discuss any impact on the quality of the drug product as a result of any changes involved. In addition provide a summary of (b) (4) of new 5 lots.

Please respond by to Drug Process comments by COB April 20, 2017.

1) email to facilitate review 2) formal submission to the NDA.

Kindly confirm receipt upon delivery.

Kristine

Kristine F. Leahy, RPh.

Regulatory Business and Process Manager

HHS | FDA | CDER

Office Of Pharmaceutical Quality (OPQ)

Office Of Program and Regulatory Operations (OPRO)

10903 New Hampshire Ave | WO75 | Room 4507 |

Silver Spring, MD 20993

Ph. 240-402-5834

Kristine.leahy@fda.hhs.gov

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Kristine.leahy@fda.hhs.gov

****FDA requires the use of secure email for all communications that may include proprietary information.
To establish, please contact secureemail@fda.hhs.gov**



Kristine
Leahy

Digitally signed by Kristine Leahy
Date: 4/12/2017 02:03:28PM
GUID: 55f72bd9003d99948f388d681cbe17d



NDA 207795

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Bausch & Lomb Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Mary Harrell, BsBM, RAC
Director, Regulatory Affairs

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA), dated and received February 24, 2017, resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latanoprostene Bunod Ophthalmic Solution, 0.024%.

We acknowledge receipt of your correspondence dated and received March 17, 2017, requesting a review of your proposed proprietary name, Vyzulta.

The target date for your proprietary name review is June 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Lois Almoza, Regulatory Project Manager, in the Office of New Drugs at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Abiola M. Olagundoye-Alawode, PharmD, MS
LCDR, USPHS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

SARAH J HARRIS
04/11/2017



NDA 207795

MEETING MINUTES

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We also refer to the teleconference between representatives of your firm and the FDA on September 1, 2016. The purpose of the meeting was to discuss the Complete Response letter dated July 21, 2016. Specifically, the Applicant seeks agreement with the proposals for the resubmission of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024% to obtain reasonable assurance of acceptance of filing and approvability.

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

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Other

Meeting Date and Time: September 1, 2016 from 10:00AM – 11:00AM (EST)
Meeting Location: Teleconference

Application Number: 207795
Product Name: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
Indication: reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension
Applicant Name: Bausch & Lomb Inc.

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

John Farley, M.D., M.P.H.	Deputy Office Director, Office of Antimicrobial Products(OAP)
Sunita Shukla, M.P.H., Ph.D.	Associate Director for Regulatory Science, (OAP)
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Derek Smith, Ph.D.	Acting Branch Chief, Office of Pharmaceutical Quality (OPQ)/ Office of Process and Facilities (OPF)/Division of Inspectional Assessment (DIA)
Chunchun Zhang, Ph.D.	Acting Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Daniel Schu, Ph.D.	Product Quality Micro Reviewer, OPS/ONDQA
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Abel Eshete, Ph.D.	Statistical Reviewer, OB/DBIV
Mahesh Ramanadham, Ph.D.	Director of Regulatory, OPQ/OPF/DIA

Andrea Norwood, Ph.D.

Florida District Office Compliance Officer, Office
of Regulatory Affairs (ORA)

Milva Melendez, Ph.D.

Consumer Safety Officer, OPQ/Office of
Surveillance (OS)

Teddi Lopez, Ph.D.

Supervisory Consumer Safety Officer, OPQ/OS

Lois Almoza, M.S.

Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Joseph Papa

Chairman and CEO

Tage Ramakrishna, M.D.

Chief Medical Officer and President, Research and
Development/Quality

Stephen Haight

Vice President, Quality

Sharon Tonetta, Ph.D.

Vice President, Regulatory Affairs

Radhakrishnan Pillai, Ph.D.

Vice President, Research and Development

William Jo, MS, Ph.D, DABT

Director, Nonclinical Research and Development

Johnson Varughese

Vice President, Clinical Services

E. Kwame Obeng, Ph.D.

Executive Director, Regulatory Affairs-CMC

Robert Koger

Executive Director, Quality, Pharma and Solutions

Mary Harrell

Director, Regulatory Affairs-Product Lead

Isabelle Lefebvre, MSc

Vice President Regulatory Affairs, Branded &
Generic Prescription Drugs, Consumer Products

Linda Galbier

Director, Regulatory Affairs-CMC

Ezra Lowe, Ph.D.

Director, Nonclinical & Clinical Pharmacology

BACKGROUND

An August 12, 2016, submission, from Bausch & Lomb Inc. (B&L) requested a meeting for NDA 207795 with the Agency regarding the Complete Response letter dated July 21, 2016. Specifically, the Applicant seeks agreement with the proposals for the resubmission of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution) 0.024% to obtain reasonable assurance of acceptance of filing and approvability.

A Meeting Request Granted letter issued on August 16, 2016. The August 12, 2016, Meeting Package was received August 12, 2016. Meeting Preliminary Comments were sent to B&L, via e-mail on, August 26, 2016. B&L forwarded talking points via e-mail on August 30, 2016. The talking points have been incorporated throughout the meeting minutes in bold italic font.

DISCUSSION

Following, in **bold font**, are the questions in the August 12, 2016, Meeting Package. The FDA responses to these questions are in *italic* font. Talking points from the Sponsor sent via e-mail on, August 30, 2016, are in **bold italic** font. Discussions that took place during the September 1, 2016, teleconference are in regular font.

QUALITY QUESTIONS

Reference is made to the Complete Response letter dated July 21, 2016, and the issues raised by the Agency regarding the recent inspection of the Bausch & Lomb Incorporated (Bausch & Lomb) manufacturing facility named in NDA 207795. Specifically, we wish to gain agreement with the Agency on the proposed plan to satisfactorily resolve the inspection deficiencies associated with the Complete Response and forthcoming resubmission of the above referenced application.

The complete discussion of the proposed plan is presented in Section 1.6.2.10.1 of the Background Materials document under Quality.

Question 1

To date, action items from the Bausch & Lomb 483 response have been completed on time, or ahead of schedule, and the remaining actions are on schedule for timely or early completion. Also the site continues to provide monthly updates to FDA's Florida District Office on each action item to show transparency of its progress. To date, the company has not received any feedback from the Florida District Office on the 483 response or the monthly updates. Bausch & Lomb would like to know if FDA is in alignment with the Company on the remediation plan to resolve the inspection observations satisfactorily? Specifically, can the Review Division, the Office of Pharmaceutical Quality and the District Office confirm whether the completed actions and ongoing activities satisfactorily address the inspectional observations or are there additional actions that must be implemented in order to close out the inspection?

FDA Response: The review of the promised corrective actions and remediation plan is ongoing. At this time, we have not identified additional actions that should be considered to close out the inspection.

You should continue to implement the corrective actions identified by your third-party consultants and by your own assessment as described in your responses to the inspectional observations. We recommend that you review all correspondence with the District Office to ensure that there are no discrepancies in the updates and that the updates clearly identify all proposed actions that have been completed and those that remain pending.

B&L Clarification Request:

We request clarification on the below statement extracted from the FDA Response to Question #1.

“We recommend that you review all correspondence with the District Office to ensure that there are no discrepancies in the updates and that the updates clearly identify all proposed actions that have been completed and those that remain pending.”

B&L would like to understand further if the Agency and/or the District have found any discrepancies in the update that is of potential concern to satisfactorily address the observations?

In addition, in the last update provided to the District Office (dated July 29, 2016) for which we have received acknowledgement, we requested a meeting with the District Office to discuss the facility's response, updates, and completed/planned remediation efforts. Will the District grant the meeting request prior to the planned resubmission?

Meeting Discussion:

The District Office stated they plan to have a meeting with the B&L shortly after this teleconference to discuss their questions including discrepancies noted to date.

Question 2

Will a reinspection of the Bausch & Lomb Tampa facility be required to close out the inspection and for the regulatory holds on applications to be lifted?

FDA Response: Given the significant observations identified during the last inspection, it is anticipated that a re-inspection will occur to verify the corrective actions at your facility.

Meeting Discussion: None

Question 3

If a reinspection is required, B&L Tampa will be prepared for the Vyzulta PAI re-inspection of (b) (4) as of November 30 2016; whereas, (b) (4) will be prepared by January 31 2017. To confirm alignment with FDA on which action items require completion before the inspection can be closed out, can the Review Division, the Office of Pharmaceutical Quality and the District Office identify those action items?

FDA Response: Please see responses to Question #1 and #2. The purpose of the anticipated inspection will be to verify corrective actions to the last inspection and to assess readiness to manufacture the application product per the application commitments. The manufacturing lines designated in the submitted application to support commercial manufacturing should be ready for inspection at the time of resubmission as the inspection can occur at any time during the review cycle. It is your responsibility to designate commercial lines for the application and ensure they are ready for inspection at the time of submission. If the desired commercial lines are not operational at the time of the inspection, this would be considered an approvability issue.

Meeting Discussion: None

Question 4

Similarly, if a reinspection is required, is the (b) (4) remediation adequate for a satisfactory reinspection and to obtain reasonable assurance of approvability of resubmitted NDA 207795? Or does (b) (4) also need to be operational?

FDA Response: Please see response to Question #3.

Meeting Discussion: None

QUESTIONS REGARDING COMPLETE RESPONSE LETTER ADDITIONAL COMMENTS

To assist in providing an adequate resubmission of the application, we wish to address the comments/recommendations that were not considered approvability issues during review of the above referenced application but were provided under “ADDITIONAL COMMENTS” in the Complete Response letter dated July 21, 2016.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC) QUESTIONS

The Agency provided additional comments/recommendations with regard to the in-use stability data provided in the original application.

Complete Response – ADDITIONAL COMMENTS #1:

The in-use stability data does not support the label storage statement (b) (4). A scientific justification was not provided to address the observed (b) (4). From the recent inspection of the Bausch and Lomb facility, we are aware of investigations into the (b) (4) issues. A definitive root cause for the (b) (4) stability failures had not been determined.

In your resubmission, we recommend that you include a copy of the protocol for the in-use stability of drug product and provide data from multiple batches analyzed for all quality attributes, including (b) (4), once every 2 weeks until the desired storage duration. Additionally, please update your submission to include any information presented in the NDA that is impacted by your actions to address the inspectional issues related to the NDA (e.g. 3.2.R Investigation Report for the (b) (4)).

The complete discussion regarding the in-use data is provided in Section 1.6.2.10.2 of the Background Materials document under Chemistry, Manufacturing and Controls.

Question 5

Are these additional in-use data sufficient for resubmission to support storage at 25°C for 8 weeks after opening?

FDA Response: The additional in-use stability data seems reasonable. We will evaluate the completeness upon the NDA resubmission.

Meeting Discussion: None

- a) **If not, please provide more detail of what the FDA reviewer expects to see (duration: every 2 weeks, all tests/criteria as shown in attached protocol, number of lots, etc.). Note as part of the response to the FDA483 (item 1.B) B&L indicated that the USP preferred (b) (4) method would be used for (b) (4) (b) (4). Therefore, any new in-use data would be generated by (b) (4) (b) (4)**

FDA Response: Refer to the above response.

Meeting Discussion: None

Question 6

Are the proposed changes in particulate matter specification acceptable?

FDA Response: The particular matter specification seems reasonable. We consider either USP method to be acceptable.

B&L Clarification Request:

We acknowledge your comment and request confirmation that the USP (b) (4) acceptance criteria as outlined in the briefing document are acceptable for use with this drug product

Meeting Discussion: (b) (4)
the Agency recommends using USP<789>.

Question 7

Do the proposed updates to the CMC section address satisfactorily the additional comments? If not, please advise.

FDA Response: The updates will be evaluated during NDA review.

Please provide the process validation data and risk assessment update. Provision of executed batch record for process validation batches would be helpful. Chemical hold time data to be obtained during the validation should be submitted if available.

In your updates to the District Office, the investigation to confirm the root cause of the (b) (4) identified in the 61 day in-use study for Lantanoprostene Bunod appears to be still open. You have committed to amend technical memo AD-2015-012 as necessary to include this information. This information will be needed to accurately assess the in-use stability data.

Meeting Discussion: None

NONCLINICAL QUESTIONS

The Agency provided additional comments/recommendations with regard to the data presented in the original application to support the pregnancy risk statements in the proposed label.

Complete Response – ADDITIONAL COMMENTS #2:

The data you have provided concerning pregnancy risk are limited (b) (4). (b) (4). Currently proposed labeling provides exposure margins based on dose multiples (on a mg/m² basis, presuming 100% absorption). To further refine the exposure margin estimates, the following could be informative:

- a. Conduct a rabbit embryofetal study by the topical ocular route to more directly address the assessment of risk for the human route of administration.
- b. Provide adequate toxicokinetic data in embryofetal development studies. Measure parent (latanoprostene bunod) and its two active metabolites (latanoprost acid and butanediol mononitrate), as well as release of nitric oxide. Assays should be sufficiently sensitive, and LLOQ adequate to capture the lowest biologically active exposure.
- c. Based on the results of item a. above, conduct a pre-/postnatal study (or peri-/post-natal study) if needed to complete the reproductive and developmental assessments.

The complete discussion regarding the nonclinical data is provided in Section 1.6.2.10.3 of the Background Materials document under Nonclinical.

Question 8

Based on the rationale provided in Section 1.6.2.10.3 of the Background Materials document, does the Agency agree that additional developmental and reproductive toxicity assessments would not be required to support future labeling revisions for this product?

FDA Response: Presuming concurrence is reached on labeling, FDA concurs that no additional nonclinical testing is required for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

B&L Clarification Request:

We acknowledge your comment “FDA concurs that no additional nonclinical testing is required for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.” However, we request clarification on the below statement extracted from the FDA Response to Question #8.

“Presuming concurrence is reached on labeling”

In the response to the Agency labeling comments (dated July 8, 2016, Sequence 0020), B&L accepted the majority of the proposed changes to the nonclinical section of the labeling. Please

clarify what information to date is of concern that we have not reached concurrence and would potentially require additional nonclinical testing.

Meeting Discussion: The Agency requested further detailed explanations/justifications for the Applicant's proposed changes from the wording proposed by the Agency.

Question 9

Does the Agency agree that the nonclinical program currently presented in NDA 207795 provides sufficient data to support the adequate review and reasonable assurance of approvability of the resubmission of the application?

FDA Response: From a nonclinical pharmacology/toxicology perspective, the package supports approval. Presuming concurrence is reached on labeling, there are no outstanding nonclinical pharmacology/toxicology issues or requests.

B&L Clarification Request:

We acknowledge your comment "From a nonclinical pharmacology/toxicology perspective, the package supports approval." However, we request clarification on the below statement extracted from the FDA Response to Question #9.

"Presuming concurrence is reached on labeling, there are no outstanding nonclinical pharmacology/toxicology issues or requests."

In the response to the Agency labeling comments (dated July 8, 2016, Sequence 0020), B&L accepted the majority of the Agency proposed changes to the nonclinical section of the labeling. Please clarify what specific information in the label is of concern that we have not reached concurrence and would potentially present an issue or require additional requests.

Meeting Discussion: See Meeting Discussion for Question 8.

REGULATORY QUESTIONS

The complete discussion regarding the Regulatory questions are provided in Section 1.6.2.10.4 of the Background Materials document under Regulatory.

Question 10

When the cGMP deficiencies noted in FDA Form 483 issued on February 25, 2016 are found to be satisfactorily addressed and remediated, will the Agency consider the approvability issue to be resolved?

FDA Response: This determination is expected to be made following the expected re-inspection.

Meeting Discussion: None

Question 11

Please confirm that ADDITIONAL COMMENTS #1 and/or #2 are not required to be addressed to achieve an acceptable filing of the resubmission to constitute a complete response to the Complete Response letter?

FDA Response: Yes

Meeting Discussion: None

Question 12

The applicant intends to resubmit NDA 207795, as a Class 1 resubmission because it meets the criteria defined in MAPP 6020.4 Revision 2. Does the Agency agree with the proposed filing category for the resubmission of NDA 207795?

FDA Response: No. The resubmission will be considered a Class 2 resubmission with a 6 month clock.

B&L Clarification Request:

We acknowledge your response. However, we would like to understand the determination of a Class 2 resubmission with a 6 month clock for review.

We respectfully request clarification on what information (data) planned to be included in this resubmission for review has redefined it as a Class 2 resubmission with a 6 month clock.

The plan for resubmission as described in the briefing document proposed cross referencing information previously reviewed by the Agency with the exception of updated data for the in-use study to support labeling.

Considering there is no further nonclinical data to be provided, the in-use stability data was not considered an approvability issue and the data provided for review would be minimal, B&L would like to understand why the resubmission would not be considered a Class 1 with a 3 month clock?

Meeting Discussion: The Agency anticipates a re-inspection;per MAPP 6020.4, “Classifying Resubmission of Original NDAs, BLAs, and Efficacy Supplements in Response to Complete Response Letters”, when a resubmission requires a re-inspection it would be considered a Class 2 resubmission.

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/s/

WILEY A CHAMBERS
09/29/2016



NDA 207795

MEETING REQUEST GRANTED

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We also refer to your August 12, 2016, correspondence requesting a meeting to discuss the Complete Response letter dated July 21, 2016. Specifically, the Applicant seeks agreement with the proposals for the resubmission of NDA 207795 for Vyzulta (latanoprostene bunod ophthalmic solution, 0.024%) to obtain reasonable assurance of acceptance of filing and approvability. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: September 1, 2016
Time: 10:00 – 11:00AM (EST)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Probable CDER Participants:

John Farley, M.D., M.P.H.	Deputy Office Director, Office of Antimicrobial Products(OAP)
Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Philip Colangelo, Pharm. D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)

Yongheng Zhang, Ph.D.
Lori Kotch, Ph.D.
Andrew McDougal, Ph.D.
Chunchun Zhang, Ph.D.

Yan Wang, Ph.D.

Yunfan Deng, Ph.D.
Diana Willard
Lois Almoza, M.S.

Clinical Pharmacology Reviewer, OCP/DCPIV
Pharmacology/Toxicology Team Leader, DTOP
Pharmacology/Toxicology Reviewer, DTOP
Acting Product Quality Team Leader, (OPQ)/Office
of New Drug Products (ONDP)
Statistical Team Leader, Office of Biometrics (OB)/
Division of Biometrics IV (DBIV)
Statistical Reviewer, OB/DBIV
Chief, Project Management Staff, DTOP
Regulatory Health Project Manager, DTOP

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Please e-mail me any updates to your attendees at Lois.Almoza@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Lois Almoza at (240) 402-5146 & Ramou Mauer at (301) 796-1600.

Please refer to the following link for visiting the White Oak Campus:

<http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/cm241748.htm>

We acknowledge receipt of the meeting package included with the meeting request. Submit 20 desk copies to me as soon as possible. If the materials presented in the meeting package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

Lois Almoza, M.S.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6241

10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Secure email is required for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

LOIS A ALMOZA
08/16/2016



NDA 207795

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

We acknowledge receipt on February 24, 2017, of your resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We consider this a complete, class 2 response to our July 21, 2015, action letter. Therefore, the user fee goal date is August 24, 2017.

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LOIS A ALMOZA
03/16/2017

From: Almoza, Lois
Sent: Wednesday, June 22, 2016 3:46 PM
To: 'Harrell, Mary E'
Subject: Draft Label - NDA 207795/Vyzulta
(latanoprostene bunod ophthalmic solution), 0.024%/
Bausch & Lomb Inc.

Hi Mary,

Please see the attached draft package insert and carton/container. Our reviews are ongoing and the PDUFA goal date for this application is July 21, 2016.

Thank you,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS A ALMOZA
06/22/2016

From: Almoza, Lois
Sent: Monday, April 04, 2016 2:59 PM
To: Harrell, Mary E (Mary.Harrell@bausch.com)
Cc: Lefebvre, Isabelle (Isabelle.Lefebvre@Valeant.com)
Subject: Information Request - NDA 207795/Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc

Good Afternoon,

Please see the information request below.

Thanks,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

1. Reference is made to the IND 73435 annual report received May 22, 2012, for the reporting period March 24, 2011 to March 23, 2012. Module 1.13.1.1 reported, 'A study entitled "9-Month Topical Ocular Instillation Toxicity and Toxicokinetic Study with PF-03187207 in Cynomolgus Monkeys" (b) (4) Study # 6348-415) was conducted by the original IND owner. However as the original sponsor was discontinuing the program, the report was finalized without all analyses (mainly histopathology) being conducted. After the program was transferred to Bausch & Lomb, the study was re-opened and the remaining evaluations were completed. A summary of the updated final report is provided below. It should be noted that the additional analysis had no significant impact on the original conclusions.'

Reference is also made to the minutes of the End of Phase 2 meeting held September 26, 2012 for IND 73435. In response to nonclinical question 1, DTOP's response included

"DTOP acknowledges receipt on June 2, 2011 of the 9-month topical ocular instillation toxicity and toxicokinetic study with PF-03187207 in cynomolgus monkeys (report # 6348-415), and also your notification in the Annual Report (AR) submitted May 22, 2012 that the study was re-opened to complete additional analyses (mainly histopathology). Although DTOP

is awaiting submission of the final revised report, based on your summary in the AR, DTOP has no nonclinical objection to the proposed Phase 3 trial. Submit the final revised report as soon as feasible, but no later than the NDA.”

Review of the NDA submission found the final report # 6348-415 dated April 12, 2011, but no additional analyses. Please either indicate where the additional analyses are located in the NDA, or provide them to the NDA. If the report was revised, provide the most current version.

2. Review of the 9-month monkey study (report # 6348-415) is ongoing. Please provide historical control information for pleural/subpleural chronic fibrosis/inflammation and related lung lesions.
3. Review of the 28-day monkey study (impurity qualification (report # 8273344) is ongoing. Clarification is requested regarding the gross observation of uncollapsed lung for treated male # I01390, described as “lung: uncollapsed; lobes, multiple; present; collected/lobes on right side”. Review noted that no histopathology findings were recorded. If available, please provide any additional information regarding the gross finding, or regarding SOPs and the protocol that would help understand why this lung was remarkably different from the others. Please provide relevant historical control data. If documented, please indicate which lobe(s) of the lung were evaluated microscopically.
4. For the 9-month monkey study (report # 6348-415), one high-dose monkey (# I04609) is reported as having a right eye intraocular pressure of 2.0 on D23 (page 597). Is this value correct? If so, please address the potential for ocular hypotony.
5. The 9-month monkey study reports individual IOP values to the tenth of a mm Hg, with the tenth value always being zero (pages 597-600), e.g. 20.0, 18.0, 19.0, 14.0. These data suggest that IOP was actually measured to the ones place. Please explain. Please indicate whether the IOP data were quality assured.
6. Regarding the final embryofetal (EFD) study reports received 3/30/2016, review noted that each report lists differences from the submitted draft report versus the final report at the end. We understand these listings to mean that no changes were made to any of the data in the summary tables (e.g. fetal abnormalities, maternal performance) or individual animal data. If any changes to the summary or raw data were made, please provide an annotated version of the final report (i.e. changes tracked).
7. Clarification is requested regarding the definitions used in the four EFD studies conducted at [REDACTED] ^{(b) (4)} for latanoprostene bunod. In non-GLP and GLP rat and rabbit EFD studies it is stated in study reports that:

A dead fetus was defined as a term fetus that did not respond to stimuli and that was not markedly autolyzed; dead fetuses demonstrating marked to extreme autolysis were considered to be late resorptions. A conceptus was defined as a late resorption if it was grossly evident that organogenesis had occurred; if that was not the case, the conceptus was defined as an early resorption.

The application of the definitions of late resorption and early resorption is not clear. For example, evidence of the initial stages of organogenesis are "grossly evident" by GD 8 or 9, if the technician is adept at removing/examining early embryos. For EFD studies in the current application, how far along in organogenesis would an embryo have to be in order for the study laboratory to consider that organogenesis was "grossly evident" and conclude that it was a late resorption. Were additional criteria (e.g. external landmarks) also used? Essentially, we are trying to determine whether late resorptions, according to your definition, would include conceptuses at embryonic stages (if so, what stages), fetal stages or both. Please clarify.

8. Clarification is requested regarding the definitions of malformation versus variation in EFD study reports. For both GLP EFD studies (report # 20073521, page 35; report # 20073523, page 33), the authors defined malformations as *"irreversible changes that occur at low incidences in this species and strain"* and defined variations as *"common findings in this species and strain and reversible delays or accelerations in development"*. Please provide further clarification, as follows.
 - a. Is it correct to conclude that the authors used the incidence rates alone to determine whether or not a particular finding is a malformation or a variation?
 - b. At what incidence threshold(s) would you consider a finding common? Which datasets (i.e. concurrent control, current/relevant historical control data) were used to make these determinations? Would all anomalies that occur at incidences below this threshold be considered malformations (excepting reversible delays or accelerations in development)?
 - c. According to your definitions, would irreversible structural changes be considered variations if indeed they were 'common'?
 - d. Does potential impact on function, survival or health factor into your determination of malformation versus variation? For example, if a commonly-found, irreversible anomaly can be reasonably expected to cause functional consequences, based on nature of finding, would it still be considered a variation according to your definition?

9. The non-GLP rat (report # 20073520) and rabbit (report # 20073522) EFD range-finding studies assessed “external abnormalities” (section 4.10.6 Fetal Examinations, of each report) but the historical control data (Appendix 11 of each report) were provided for “fetal gross external alterations”. Please verify that the terms abnormalities and alterations are exact synonyms, or explain what differences these words are intended to convey.

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/s/

LOIS A ALMOZA
04/04/2016



NDA 207795

INFORMATION REQUEST

Bausch & Lomb, Inc.
Attention: Isabelle Lefebvre
Sr. Director, Branded Rx and Gx Product Portfolio
400 Somerset Corporate Center
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesneo® (latanoprostene bunod) 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 March 11, 2016, in order to continue our evaluation of your NDA.

Drug Product:

1. The excipient, polysorbate 80 (b) (4) is used in the proposed commercial formulation as described in the NDA submission. The clinical material and the primary stability batches also used polysorbate 80 (b) (4) in the manufacture of the drug product. In the context of the above, we note your comment in Section 3.2.P.2.2 that (b) (4) (b) (4) for the commercial formulation. Please clarify the context of this statement. Note that any changes to the formulation, manufacturing process and/or container closure used in the pivotal clinical trial may require additional studies.
2. We acknowledge your response dated on 12/23/2015 on the in-use evaluation study. The response does not provide adequate justification for the observed OOS for (b) (4) and therefore does not support the proposed in-use period. We recommend that you submit the data requested from earlier time points and/or data from additional batches over several time points to justify the requested in-use time period.

If you have any questions, call me at (240) 204-8578.

Sincerely,

Erin Andrews -A

Digitally signed by Erin Andrews A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Erin Andrews A
09 2342 19200300 100 1 1=2001366614
Date: 2016.02.29 11:51:17 -0500

Erin Andrews, Pharm.D
Regulatory Business Process Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



NDA 207795

INFORMATION REQUEST

Bausch & Lomb, Inc.
Attention: Isabelle Lefebvre
Sr. Director, Branded Rx and Gx Product Portfolio
400 Somerset Corporate Center
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesneo® (latanoprostene bunod) 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 March 11, 2016, in order to continue our evaluation of your NDA.

Microbiology Comment:

Please provide the following information or a reference to its location in the NDA 207795:

1. With regard to the (b) (4) sterilization validation studies for the container closure system components to be used in the commercial production of the drug product:



(b) (4)

d.

5. The FDA is aware of issues with antimicrobial effectiveness testing (AET) failures of multiple dose topical ophthalmic products preserved with benzalkonium chloride despite the products meeting the benzalkonium chloride content specification. The cause of these AET failures is presently unknown and the FDA is requesting additional information regarding preservative effectiveness testing for some multiple dose topical ophthalmic products in order to ensure that the preservative is not only present, but effective throughout the product shelf-life. The agency is requesting further testing until a consistent history of passing AET at expiry has been established. Once established, a modified stability test schedule may be requested of the Agency. Please provide the following information:
- a. Provide all the AET results for the drug product up to and including the proposed expiry for the three registration stability lots.
 - b. Include AET as a routine test for all stability lots per the registration batch test schedule.

If you have any questions, call me at (240) 204-8578.

Sincerely,

Erin Andrews

-A

Digitally signed by Erin Andrews - A
DN: c=US, o=U.S. Government, ou=HH5,
ou=FDA, ou=People, cn=Erin Andrews -
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Date: 2016.02.19 15:08:46 -05'00'

Erin Andrews, Pharm.D
Regulatory Business Process Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207795

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bausch & Lomb, Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Mary Harrell, BsBM, RAC
Associate Director, Branded Rx and Gx Product Portfolio
US Regulatory Affairs

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA), dated and received, July 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latanoprostene Bunod Ophthalmic Solution, 0.024 %.

We also refer to your correspondence, dated and received, October 30, 2015, requesting review of your proposed proprietary name, Vyzulta.

We have completed our review of the proposed proprietary name, Vyzulta and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 30, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Lois Almoza, Regulatory Project Manager in the Office of New Drugs, at 240-402-5146.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

TODD D BRIDGES
01/15/2016

From: Almoza, Lois

Sent: Wednesday, January 06, 2016 11:06 AM

To: Harrell, Mary E (Mary.Harrell@bausch.com); Isabelle.Lefebvre@bausch.com

Subject: Information Request - NDA 207795/Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc

Good Morning,

Please see the information request below.

For active IND 73435, the Annual Report submitted May 19, 2015, reported that three studies were ongoing: # PH14005 [Effect of LBN on aqueous humor dynamics in ocular hypertensive primates]; # 20073520 [A dose range-finding embryo-fetal development study of latanoprostene bunod (LBN) by intravenous (bolus) in rats]; and # 20073522 [A dose range-finding embryo-fetal development study of latanoprostene bunod (LBN) by intravenous (bolus) in rabbits].

Please provide a timeline for submission of the reports for these studies. We request that the reports be submitted to the NDA as soon as feasible.

Thank you,

Lois

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

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/s/

LOIS A ALMOZA
01/06/2016

**PeRC Meeting Minutes
December 2, 2015**

PeRC Members Attending:

Lynne Yao

Linda Lewis

Lily Mulugeta

Thomas Smith

Dionna Green

Gerri Baer

Daiva Shetty

Meshaun Payne

Shrikant Pagay

Belinda Hayes

Michelle Roth-Cline

George Greeley

Hari Cheryl Sachs NON-RESPONSIVE

Dianne Murphy NON-RESPONSIVE

Barbara Buch NON-RESPONSIVE

Adrienne Hornatko-Munoz NON-RESPONSIVE

Wiley Chambers

Greg Reaman NON-RESPONSIVE

Maura O'Lear

Agenda

9:00	NON-RESPONSIVE				
9:30	NON-RESPONSIVE				
9:50	NON-RESPONSIVE				
10:10	NON-RESPONSIVE				
10:30	NON-RESPONSIVE				
10:50	NON-RESPONSIVE				
11:00	NON-RESPONSIVE				
11:20	NON-RESPONSIVE				
11:30	NON-RESPONSIVE				
11:40	NON-RESPONSIVE				
11:50	NDA 207795	Veseno (latanoprostene) Full Waiver with Agreed iPSP	DTOP	Lois Almoza	Glaucoma
	NON-RESPONSIVE				

5 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

Vesneo (latanoprostene) Full Waiver (with Agreed iPSP)

- Proposed Indication: Glaucoma
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver in pediatric patients because there are too few patients with disease/condition to study.

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/s/

GEORGE E GREELEY
12/15/2015



NDA 207795

MID-CYCLE COMMUNICATION

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We also refer to the teleconference between representatives of your firm and the FDA on December 14, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

William M. Boyd, MD
Cross Discipline Team Leader
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 14, 2015 from 1:20 – 2:00PM (EST)

Application Number: NDA 207795

Product Name: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%

Indication: reduction of intraocular pressure for patients with open-angle glaucoma of ocular hypertension

Applicant Name: Bausch & Lomb Inc.

Meeting Chair: William M. Boyd, M.D.

Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

John Farley, M.D.	Deputy Director, Antimicrobial Products
Wiley A. Chambers, M.D.	Deputy Director, DTOP (DTOP)
William Boyd, M.D.	Cross Discipline Team Leader (CDTL), DTOP
Jennifer Harris, M.D.	Clinical Reviewer, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Philip Colangelo, Pharm. D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Mary Lewis, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Anamitro Banerjee, Ph.D.	Product Quality Team Leader, Office of Pharmaceutical Science (OPS)/ Office of New Drug Quality Assessment (ONDQA)/Branch V
Daniel Schu, Ph.D.	Product Quality Micro Reviewer, OPS/ONDQA
Abel Eshete, Ph.D.	Statistical Reviewer, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Carolyn Yancey, M.D.	REMS Reviewer, Office of Surveillance and Epidemiology (OSE)
Michelle Rutledge, Ph.D.	Pharmacist, OSE
Roy Blay, Ph.D.	Reviewer, Office of Scientific Investigations
Marc Goldstein	Independent Assessor, Eastern Research Group
Meena Ramachandra, PhD.	Pharmacist, Office of Prescription Drug Promotion
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

BAUSCH & LOMB INC. ATTENDEES

Tage Ramakrishna, MD	Chief Medical Officer & Head R&D
Sharon Tonetta, PhD	Vice President, Regulatory Affairs
Isabelle Lefebvre, MSc.RA	Vice President, Regulatory Affairs
Mary Harrell, BsBM	Associate Director, Regulatory Affairs
Kwame Obeng, PhD, MSE	Executive Director, Regulatory Affairs - CMC
Linda M Galbier	Senior Manager, Regulatory Affairs – CMC
Shankar Swaminathan, PhD	Associate Director, Regulatory Affairs - CMC
Marianna Halari	Director Programs, Regulatory Affairs
Kathleen Krenzer, OD, PhD, DABT	Senior Principal Scientist, Nonclinical Safety/Toxicology
Ezra Lowe, PhD	Senior Manager, Nonclinical & Clinical Pharmacology
Johnson Varughese	Vice President, Clinical Services
Robert Israel, MD	Vice President, Clinical and Medical Affairs
Jason Vittitow, PhD	Director, Clinical Operations
Robert Kang	Senior Director, Data Management/Statistics
Mark Powell	Data Management/Statistics
Binu Alexander, MD	Senior Director, Clinical Operations
Saberi Rana Ali, MBBS, MD (Ophth.), MPH	Director, Global Pharmacovigilance & Risk
Philip Sturno	Vice President, Product Development

1. INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2. SIGNIFICANT ISSUES

To date, no significant review issues have been identified.

3. INFORMATION REQUESTS

Currently no outstanding information requests.

The Division noted that the clinical study report for Study 874 regarding the effect of the proposed product on methemoglobin concentrations in humans has not been submitted. Bausch & Lomb stated they expect the report to be submitted in January 2016.

The Division also noted that two nonclinical embryofetal study reports are pending; audited draft reports for the studies were expected at the end of December 2015. Bausch & Lomb stated the studies would be completed at the end of December 2015, and they would follow-up with the Division on estimated submission times for draft reports.

CMC anticipates sending a new information request to Bausch & Lomb either today or tomorrow after the request has been finalized.

4. MAJOR SAFETY CONCERNS/RISK MANAGEMENT

To date, no major safety concerns or need for REMS have been identified.

5. ADVISORY COMMITTEE MEETING

To date, the Division has no plans to request an Advisory Committee Meeting.

6. LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Two potential dates were offered to Bausch & Lomb Inc. for the late-cycle meeting:

April 4, 2016, 1:20-2:00 PM, EST or
April 8, 2016, 10:20-11:00AM, EST

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/s/

WILLIAM M BOYD
01/04/2016



NDA 207795

INFORMATION REQUEST

Bausch & Lomb, Inc.
Attention: Isabelle Lefebvre
Sr. Director, Branded Rx and Gx Product Portfolio
400 Somerset Corporate Center
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vesneo® (latanoprostene bunod) 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 January 04, 2016, in order to continue our evaluation of your NDA.

Drug Substance:

1. The DMF (b) (4) is currently inadequate. A list of deficiencies was sent to the DMF holder on November 23, 2015. The DMF holder must address these deficiencies before this NDA may be approved.

Drug Product:

2. Provide data on the levels of EDTA concentration in the drug product over shelf life.
3. The statement in your labeling section, (b) (4) (b) (4) is not supported by the in-use stability data submitted in the NDA. We note that at (b) (4) it is out of specification for (b) (4). Please provide data from additional time points (such as (b) (4)). Also indicate how many samples were tested.

Microbiology:

4. The proposed post-approval stability protocol and stability commitment states that (b) (4) (b) (4). The Agency disagrees with this statement. ICH Q1A (R2) section 2.2.6. states that products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life. Modify the post-approval stability protocol for AET to reflect ICH recommendations.

Process:

5. It is noted that several pages were missing in one of your batch records. Resubmit the batch record identified as a document # DBM504-K-00 ((b) (4) lot # 16803).

6.



If you have any questions, call me at (240) 204-8578.

Sincerely,

Erin
Andrews -A

Digitally signed by Erin Andrews A
DN: c=US, o=U S Government,
ou=HHS, ou=FDA, ou=People,
cn=Erin Andrews A
0 9 2342 19200300 100 1 1=200136
6614
Date: 2015.12.14 15:33:01 -05'00'

Erin Andrews, Pharm.D
Regulatory Business Process Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: 207795

PRODUCT PROPRIETARY NAME: Vesneo 0.024% ESTABLISHED/GENERIC NAME: latanoprostene bunod ophthalmic solution

APPLICANT/SPONSOR: Bausch & Lomb Inc.

PREVIOUSLY APPROVED INDICATION/S:

- (1) _____
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
- (2) _____
- (3) _____
- (4) _____

BLA/NDA STAMP DATE: July 21, 2015

PDUFA GOAL DATE: July 21, 2016

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?

Did the sponsor submit an Agreed iPSP? Yes No

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes No

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes No

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***
- Pediatric Record***

1. Pediatric age group(s) to be waived: All pediatric age groups (i.e. birth to 17 years of age)
2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.***)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. Provide justification for Waiver:

Because of the low prevalence of ocular hypertension or glaucoma in the pediatric population, the recruitment for and conduct of a clinical trial would be challenging. Furthermore, it will not be practically feasible to further explore the relative effects of latanoprostene bunod as monotherapy for pediatric glaucoma of different causes or subtypes.

Medical therapy of pediatric glaucoma is indicated for short term use to decrease or stabilize the IOP while awaiting definitive surgical repair.

There are potential safety concerns related to long term administration of prostaglandin agonists in infants during development such as increased iris pigmentation following chronic use and other ocular changes such as periorbital and eyelid changes leading to deepening of eyelid sulcus, and blue gray discoloration of the lower eyelid.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Safety and effectiveness of VESNEO in pediatric patients have not been established.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

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/s/

LOIS A ALMOZA
10/28/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207795

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Bausch & Lomb, Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Isabelle B. Lefebvre, MSc.RA, RAC EU & US
Sr. Director, Branded Rx and Gx Product Portfolio

Dear Ms. Lefebvre:

Please refer to your New Drug Application (NDA) dated and received July 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Latanoprostene bunod Ophthalmic Solution, 0.024 %.

We also refer to your correspondence, dated and received, July 21, 2015, requesting review of your proposed proprietary name, Vesneo.

We have completed our review of the proposed proprietary name, Vesneo, and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Vesneo, is orthographically similar to the currently marketed name Visine (tetrahydrozoline hydrochloride), and shares product characteristics that may increase the risk for name confusion and wrong drug errors. The orthographic similarity of this name pair stems from the fact that these two names are similar in length (6 letters) and shape. Additionally, both names share the letter V and s in the first and third positions, respectively. Furthermore, the second letter 'e' in Vesneo and 'i' in Visine may appear similar to each other when scripted. Thus, the beginnings of the names are almost identical ('Ves' vs 'Vis'). Additionally the ending letter strings (ine vs. neo) also look similar when scripted. Although Visine is available in multiple formulations (i.e., Visine-A, Visine AC, and Visine L.R) and is usually written with a modifier, the original formulation can be prescribed without any modifier and can therefore be simply written as "Visine".

The orthographic similarity of this name pair is further supported by FDA's Phonetic and Orthographic Computer Analysis (POCA) System, which calculates 64% orthographic for this name pair.

In addition to orthographic similarities, these two products have overlapping product characteristics. Both products are ophthalmic formulations, have an overlapping dose (1 drop), are administered via ophthalmic routes and may be administered once daily. We acknowledge that Vesneo and Visine have different strengths (0.024% vs. 0.05%). However, since these products are available in single strength only, the product's strength can be omitted on a prescription. Thus, the differences in strength between Vesneo and Visine may not always prevent name confusion. Our postmarketing experience shows that when there is compelling orthographic similarity amongst product names, errors may still occur despite different product strengths, for example, medication error between

Durezol (difluprednate ophthalmic emulsion) 0.05% and Durasal (salicylic acid) 26% have been reported due to similarities between this name pair¹.

We note that Visine is an over the counter product, however, our post marketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and over-the-counter drug products².

Furthermore, since Visine has been on the market for a long time, the familiarity with this name may cause confirmation bias (seeing that which is most familiar, while overlooking any disconfirming evidence). Confirmation bias has been identified as a major contributing factor to confusion between products that are orthographically similar.

We acknowledge that our conclusion differs from that of the external study submitted in support of the proposed proprietary name. Although [REDACTED] ^{(b) (4)} identified Visine as a name of concern due to the high score on the POCA analysis, and due to participants of simulation prescription study noting similar appearance between Vesneo and Visine), they did not consider Visine to be a potential source of confusion due to differences in indication, strengths, unit of measure/dosage units (i.e., mL for Vesneo versus mg for Visine), product packaging size, storage conditions, and usual dose. However, indications, product packaging or storage is not typically noted on a prescription order so these differences between the products may not mitigate the risk of confusion. As noted previously, both products can be written without identifying the product strength with directions as “use as directed, #1” or “1 drop daily as directed, dispense 1 bottle”, thereby minimizing any difference between the products.

Additionally, we note our current findings differ from our previous review of the proposed proprietary name, Vesneo, as communicated in the Conditionally Acceptable letter dated June 4, 2014. The reason we have reached a different determination with respect to the safety of the proposed name is based upon new safety information. Our previous review noted that all Visine products were marketed with a modifier. However, further evaluation of the Visine line of products and preliminary drug use data indicate the product Visine Original is prescribed as Visine without a modifier. Thus, the new information garnered caused us to revisit in this evaluation our previous Failure Modes and Effects Analysis of the Vesneo/Visine name pair. After further consideration of Visine’s and Vesneo’s product characteristics, the orthographic similarity between these proprietary names and our post-marketing experience, we believe the proposed proprietary name, Vesneo, is vulnerable to confusion with the currently marketed product, Visine.

¹ ISMP Medication Safety Alert! Acute Care. Safety Briefs: Dangerous name pair. Vol 14, No 22 November 2009; Page 3-4

² Our post marketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and over-the-counter drug products.

Rx product	OTC product	ISMP article citation
sertraline	cetirizine	Institute for Safe Medication Practices. Safety briefs: Sound-alike names. ISMP Med Saf Alert Community/Ambulatory Care. 2009; 8(9): 1-7.
benazepril	Benadryl	Institute for Safe Medication Practices. Safety briefs: Benazepril confused with Benadryl. ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.
sotalol	Sudafed	Institute for Safe Medication Practices. Safety briefs: Sudafed-Sotalol mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2006; 5(5): 1-5.
Mucomyst	Mucinex	Institute for Safe Medication Practices. Safety briefs: Mucinex-Mucomyst: Too close for comfort. ISMP Med Saf Alert Community/Ambulatory Care. 2005; 4(1): 1-4.
Mirapex	Miralax	Institute for Safe Medication Practices. Safety briefs: Mirapex and Miralax confusion. ISMP Med Saf Alert Acute Care. 2002;7(20):1-3.
Cozaar	Colace	Institute for Safe Medication Practices. Safety briefs: More on confirmation bias. ISMP Med Saf Alert Acute Care. 1996;1(23):1-2.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Lois Almoza, Regulatory Project Manager in the Office of New Drugs, at 240-402-5146.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

TODD D BRIDGES
10/19/2015



**METHODS VALIDATION
MATERIALS RECEIVED**

NDA 207795

Bausch and Lomb, Inc.
Attention: Isabelle Lefebvre
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Isabelle Lefebvre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Latanoprostene Bunod Ophthalmic Solution, 0.024%, and to our September 9, 2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 2, 2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
10/06/2015



NDA 207795

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Bausch & Lomb Inc.
Attention: Isabelle B. Lefebvre, MSc.RA, RAC EU &US
Sr. Director, Branded Rx and Gx Product Portfolio
US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your New Drug Application (NDA) dated and received on July 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vesneo (latanoprostene bunod ophthalmic solution), 0.024%.

We also refer to your amendments dated August 28 and September 16, 2015.

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 July 21, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

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, mid-cycle, 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 31, 2016.

In addition, the planned date for our internal mid-cycle review meeting is December 8, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

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.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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.

REQUIRED PEDIATRIC ASSESSMENTS

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. We acknowledge receipt of your request for a full waiver of pediatric studies for this application.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
09/29/2015

From: Bhandari, Navi
To: "isabelle.lefevre@bausch.com"
Bcc: [DiGiulio, Denise M.](#); [Banerjee, Anamitro](#); [Almoza, Lois](#)
Subject: NDA 207795 Information Request 9/28/2015
Date: Monday, September 28, 2015 8:50:00 AM
Importance: High

Good Morning Isabelle,

My team has asked that I convey the following comments to you. Please provide an email response back confirming receipt.

Please indicate what type of testing the following 3 contract labs will be providing (i.e. finished product, excipient, stability, API) and the names of the tests.



Thank you,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

CDER/FDA
240-402-3815

From: Almoza, Lois

Sent: Wednesday, September 16, 2015 1:23 PM

To: Isabelle.Lefebvre@bausch.com

Subject: Information Request - NDA 207795/Vesneo (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc.

Good Afternoon Isabelle,

Please respond to the following information request by September 29, 2015.

1. We note in Section P.2 that (b) (4) configurations (b) (4) 5 mL fill in 7.5 mL bottle) are available for commercial use; however, P.7 notes 5 mL fill in 7.5 mL bottle as the only commercial configuration. Please confirm the commercial configuration and revise the NDA sections as appropriate.

2. For the environmental assessment section, no statement regarding extraordinary circumstances was provided, per 21 CFR 25.15(a) and (d).

Thanks,

Lois

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

Fax: 301-796-9881

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/s/

LOIS A ALMOZA
09/16/2015

From: Almoza, Lois

Sent: Tuesday, September 15, 2015 9:40 AM

To: Isabelle.Lefebvre@bausch.com

Cc: Willard, Diana M

Subject: Information Request - NDA 207795/Vesneo (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc.

Good Morning,

Please see the following information request below and respond by October 6, 2015.

Please provide the location of the following ANCOVA and ANOVA analyses for the Intent-to-Treat population with LOCF and Per Protocol population observed cases in Studies 769 and 770:

- Baseline mean IOP at each time point (i.e., mean IOP at 8AM, 12PM and 4PM) for each treatment group
- Upper and lower 95% CI for the mean difference in IOP at each time point at Baseline (i.e., mean IOP latanoprostene bunod minus timolol maleate at Baseline 8AM, Baseline 12PM and Baseline 4PM)

If these analyses have not been performed, please submit.

Thank you,

Lois

[Lois Almoza, M.S.](#)

[Regulatory Health Project Manager](#)

[Division of Transplant and Ophthalmology Products](#)

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

Fax: 301-796-9881

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/s/

LOIS A ALMOZA
09/15/2015



**REQUEST FOR METHODS
VALIDATION MATERIALS**

NDA 207795

September 9, 2015

Bausch and Lomb, Inc.
Attention: Isabelle Lefebvre
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Isabelle Lefebvre:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Latanoprostene Bunod Ophthalmic Solution, 0.024%.

We will be performing methods validation studies on Latanoprostene Bunod Ophthalmic Solution, 0.024%, as described in NDA 207795.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

3.2.S.4.2 (C-1928): Assay and Related Substances by UPLC

3.2.S.4.2 (C-1929):  (b) (4)

3.2.P.5.2 (C-1876): Assay and Related Substances by UPLC

Samples and Reference Standards

2 vials 1g Latanoprostene Bunod drug substance

2 vials 1g Latanoprostene Bunod reference standard

30 bottles Latanoprostene Bunod drug product (samples)

500 mg  (b) (4)

500 mg  (b) (4)

200 mg All other listed impurities and related substances (as available)

Equipment

 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
09/09/2015

From: Almoza, Lois
Sent: Friday, August 28, 2015 3:44 PM
To: 'Lefebvre, Isabelle'
Cc: Willard, Diana M
Subject: Information Request - NDA 207795/Vesneo (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc.

Good Afternoon Isabelle,

Please respond to the information request attached as soon as possible.

Thank you,

Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146

1. Please submit the SAS programs you used to perform all safety and efficacy analyses including sensitivity analyses together with proper documentations for each study separately and the pooled analysis in order for us to be able to replicate the reported results in your submitted study reports.
2. In the adiop.xpt dataset, we have identified subjects with two different IOP measurements for the same week and time point for the study eye. Although the duplicate measurements have the same magnitude for some of these subjects, for others, the IOP measurements are of different magnitudes for the same week and time point (See Table 2). We have also noticed that one subject (7708592951027) has two different baseline measures for each analysis time point. Please check for similar subjects and clarify how these measurements were used in the primary efficacy analyses and submit the updated datasets from which the results of the primary efficacy analyses are produced.
3. Please submit the results of the primary efficacy analysis for the ITT (all randomized subjects) for each pivotal study separately. Please use the treatment-time-specific worst case imputation you applied to the pooled data for subjects who do not have any post-baseline measurement and subjects who still have missing data after the LOCF approach.
4. The reason for study discontinuation for some subjects as indicated in the adsl.xpt appears to imply that these subjects might have discontinued the study due to lack of efficacy. For example subject 7706654741396 discontinued the study because his/her IOP was greater than 32 mm Hg. Please provide an updated disposition table with reasons for discontinuation related to increased IOP or IOP that cannot be lowered by the respective treatment listed as "lack of efficacy". Additionally, some subjects who were discontinued from the study due to randomization error should be put under "randomization error" with an explanation provided as a footnote. Please include the remaining reasons for discontinuation not specified in the other categories to "Others" and provide a description in the footnote (see mock up Table 1).

5. In the disposition table for study 770, one subject is listed as “ongoing in the efficacy phase”. Please provide the unique subject identifier for this subject and clarify whether or not the outcomes from this subject were used in the safety and efficacy summaries submitted in the study report.

Table 1: Patient Disposition for the Entire Study (All randomized Subjects)

	Studies			
	769		770	
	BOL-303259-X N=286	Timolol N=134	BOL-303259-X N=283	Timolol N=137
Completed Efficacy Phase				
Discontinued Efficacy Phase				
Ongoing in Efficacy Phase				
Primary Reason for discontinuation in efficacy phase				
Withdraw Consent				
Lack of Efficacy ¹				
Lost-to-Follow-up				
Randomization error ²				
Administrative Issue				
Adverse Events				
Investigator decision				
Failure to follow the required study procedures				
Other ³				

Lack of Efficacy¹ (IOP > 32 at 8:00 at Visit 4, IOP greater than 32, Per protocol subjects are to be discontinued for IOPs > / = 32mmHg however NCS per PI.) Randomization error² (subject failed inclusion#7 and was randomized by mistake, Randomized in error (inclusion criteria 7, Subject washout shorter than needed and was randomized by mistake, Randomized in error (inclusion criteria 7) Other³ (Subject Discontinued due to Amend. 1 Exclusion #2 change.)

Table 2: List of subjects with duplicate IOP measurements of different magnitude per analysis time

Subject Identified	Visit	Time	IOP Duplicates	
			IOP 1	IOP 2
7691400691219	Week 2	12 PM	20.5	26.0
7691601511083	Week 6	12 PM	12.0	15.0
7691601511083	Week 6	8 AM	12.0	18.0
7692301471582	Week 2	4 PM	20.0	20.5
7692301471582	Week 2	8 AM	22.0	22.5
7692307911454	Month 3	8 AM	13.5	14.0
7693001491396	Week 6	12 PM	22.0	23.5
7693001491396	Week 6	8 AM	22.0	24.0
7693008041337	Week 6	12 PM	13.0	15.0
7693008041337	Week 6	4 PM	14.0	16.0
7693008041337	Week 6	8 AM	13.0	14.0
7693008041345	Week 6	12 PM	22.0	24.0
7693008041345	Week 6	4 PM	20.0	22.0
7694906211243	Week 6	12 PM	14.0	15.0
7694906211243	Week 6	4 PM	14.0	15.5
7694906211243	Week 6	8 AM	13.5	15.0
7697563881246	Week 6	8 AM	18.0	22.0
7697843611294	Week 6	12 PM	15.0	17.0
7697843611294	Week 6	4 PM	16.0	18.0
7697843611294	Week 6	8 AM	16.0	18.0
7702105801476	Week 6	12 PM	19.5	21.5
7702105801476	Week 6	4 PM	19.5	22.5
7702105801476	Week 6	8 AM	25.0	30.0

7702803841363	Week 6	8 AM	22.0	22.5
7702905881423	Month 3	12 PM	11.0	12.0
7702905881423	Month 3	4 PM	11.0	13.0
7702905881423	Month 3	8 AM	12.0	13.0
7703005121455	Week 6	8 AM	18.5	20.0
7704986131435	Week 6	12 PM	14.0	16.0
7704986131435	Week 6	4 PM	14.0	15.0
7704986131435	Week 6	8 AM	17.0	19.5
7705116011126	Month 3	12 PM	12.5	18.5
7705116011126	Month 3	4 PM	12.5	17.5
7705116011126	Month 3	8 AM	15.5	18.5
7705116011126	Week 2	12 PM	12.5	18.5
7705116011126	Week 2	4 PM	12.5	17.5
7705116011126	Week 2	8 AM	15.5	18.5
7705116011126	Week 6	12 PM	12.5	18.5
7705116011126	Week 6	4 PM	12.5	17.5
7705116011126	Week 6	8 AM	15.5	18.5

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/s/

LOIS A ALMOZA
08/28/2015

From: Almoza, Lois
Sent: Tuesday, August 18, 2015 8:07 AM
To: Isabelle.Lefebvre@bausch.com
Cc: Willard, Diana M
Subject: Information Request - NDA 207795/Vesneo (latanoprostene bunod ophthalmic solution), 0.024%/ Bausch & Lomb Inc.

Good Morning Isabelle,

Please respond to the request below by August 28, 2015.

Regarding Studies 770 and 769: Please provide tables similar to those found in Section 16.1.4 of the study reports but which list the site number, number of randomized subjects by study drug and by control at that site, principal investigator and address, and any subinvestigators.

Thank you,

Lois Almoza

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

LOIS A ALMOZA
08/18/2015



NDA 207795

NDA ACKNOWLEDGMENT

Bausch & Lomb Inc.
Attention: Isabelle B. Lefebvre, MSc.RA, RAC EU & US
Sr. Director, Branded Rx and Gx Product Portfolio
US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

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: Vesneo (latanoprostene bunod ophthalmic solution), 0.024%

Date of Application: July 21, 2015

Date of Receipt: July 21, 2015

Our Reference Number: NDA 207795

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 September 19, 2015, in accordance with 21 CFR 314.101(a).

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

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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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LOIS A ALMOZA
07/31/2015



IND 73435

MEETING MINUTES

Bausch & Lomb Incorporated
Attention: Isabelle Lefebvre
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for latanoprostene bunod ophthalmic solution, 0.024%.

We also refer to the teleconference between representatives of your firm and the FDA on February 9, 2015. The purpose of the meeting was to discuss the overall organization of the NDA with a focus on addressing specific questions related to filing and format issues.

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

If you have any questions, call Eithu Z. Lwin, Regulatory Project Manager at (301) 796-0728.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
Sponsor's presentation



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 9, 2015 from 11:00 AM to 12:00 PM (EST)
Meeting Location: Teleconference

Application Number: IND 73435
Product Name: latanoprostene bunod ophthalmic solution, 0.024%.
Indication: Reduction of elevated intraocular pressure
Sponsor/Applicant Name: Bausch & Lomb Incorporated

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Eithu Z. Lwin, PharmD

FDA ATTENDEES

Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Leader
Rhea Lloyd, Clinical Reviewer
Lori Kotch, Pharmacology/Toxicology Team Leader
Andrew McDougal, Pharmacology/Toxicology Reviewer
Anamitro Banerjee, Product Quality Team Leader
George Lunn, Product Quality Reviewer
Robert Mello, Product Quality Microbiology Reviewer
Yan Wang, Statistics Team Leader
Abel Eshete, Statistics Reviewer
Philip Colangelo, Clinical Pharmacology Team Leader
Gerlie Gieser, Clinical Pharmacology Reviewer
Eithu Z. Lwin, Regulatory Health Project Manager
Robert Kalesnik-Orszulak, Pharmacy Student

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese, Independent Assessor from Eastern Research Group

SPONSOR ATTENDEES

Linda Galbier, Sr. Manager, Regulatory Affairs-CMC
Marianna Halari, Project Manager, Director Regulatory Affairs
(b) (4) Consultant for Valeant
Isabelle Lefebvre, Director, Regulatory Affairs

Maria Fortuna-Nevin, Manager, Regulatory Affairs-CMC
E. Kwame Obeng, Executive Director, Regulatory Affairs-CMC
Matthew Robben, Sr. Principal Scientist, Pharmaceutical Technical Services
Mary Richardson, Executive Director, Preclinical Development
Baldo Scassellati Sforzolini, Vice-President, Development, Eye Care
Philip Sturno, Vice-President Product Development
Sharon Tonetta, Vice-President, Regulatory Affairs
Johnson Varughese, Executive Director, Clinical Development
Jason Vittitow Director, Clinical Affairs

BACKGROUND

Bausch and Lomb Incorporated (B&L) is developing latanoprostene bunod ophthalmic solution, 0.024%, a nitric oxide donating prostaglandin F₂-alpha receptor agonist, for the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Latanoprostene bunod was licensed to B&L by Nicox in April 2010. Prior to B&L licensing latanoprostene bunod, Pfizer conducted two Phase 2 studies (Study A9441001 and Study A9441003). B&L conducted an additional Phase 2 dose ranging study (Study #659), which identified latanoprostene bunod 0.024% administered 1 drop in the evening as the safest and most effective dose. A second Phase 2 study (Study 803) was conducted to compare the effect of latanoprostene bunod 0.024% dosed once daily in the evening with timolol maleate 0.5% dosed twice daily in reducing diurnal IOP. Two phase 1 studies (Studies 809 and 849) evaluated the systemic exposures to the parent drug and its metabolites following repeated topical ocular dosing in healthy subjects. Two global Phase 3 studies (Studies 770 and 769) to evaluate the safety and efficacy of the proposed product. Study 770 has been completed and Study 769 is still ongoing. A Japanese Phase 3 study (Study 811) is still ongoing to evaluate the long-term safety of the proposed product.

An End-of-Phase 2 meeting was held on September 26, 2012. A December 12, 2014, correspondence from B&L requested a Pre-NDA meeting to discuss the overall organization (i.e. format and content) on the proposed NDA data package to support the filing of NDA submission for latanoprostene bunod ophthalmic solution, 0.024% for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

A Meeting Request Granted letter was issued on December 23, 2014. The Electronic Meeting Package was submitted and received on January 8, 2015. Meeting Preliminary Comments were sent, via e-mail, February 4, 2015. Sponsor clarifications from the meeting preliminary comments were received, via e-mail, February 8, 2015 and outlined that B&L would like further discussion during the teleconference on February 9, 2015, for Nonclinical Q1; Clinical Q1-Q2c; Quality/CMC Q2c, Q3c.

DISCUSSION

Following, in **bold**, are the questions submitted in the January 8, 2015, Meeting Package. The FDA preliminary responses to these questions sent via e-mail on February 4, 2015, are in *italics*. The Sponsor's presentation with follow-up comments and questions sent via email on February

8, 2015 is attached at the end. Discussions that took place during the February 9, 2015, teleconference are in regular font.

NON-CLINICAL

Non-Clinical Question 1: Bausch & Lomb would like to confirm that the NDA will include authorization of right of reference of Pfizer and Nicox nonclinical data to be cited for latanoprost acid, 4-hydroxybutyl nitrate and nitric oxide. Summaries of literature review and nonclinical data developed by Pfizer, Nicox and B&L including but not limited, to primary and secondary pharmacology, toxicity, genotoxicity and carcinogenicity studies conducted with (b) (4) latanoprostene bunod, latanoprost, (b) (4) will be provided in the NDA.

After review of our proposed content, does the Agency consider the approach taken meets their expectations to support filing and registration of latanoprostene bunod 0.024% QD ophthalmic solution for the intended use and administration?

FDA Response:

It is not clear from the briefing package how you intend to describe the potential for developmental and reproductive toxicity in the label, or what exposure margins you will propose. Based on FDA's previous reviews of the information you plan to reference, and current policy, FDA recommends testing latanoprostene bunod in GLP embryofetal studies in two relevant nonclinical species (with adequate evaluation of toxicokinetics) to support the NDA submission. See the Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and the Guidance for Industry S5 Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065007.htm>).

Based on the information submitted previously in the IND, and based on your confirmation that the NDA will include authorization of right of reference of Pfizer and Nicox's nonclinical data for latanoprost acid, 4-hydroxybutyl nitrate and nitric oxide, FDA concurs that the other nonclinical data appear adequate to support filing. The adequacy of the nonclinical data to support the NDA will be a review issue.

Meeting Discussion:

For new molecular entities (NMEs), FDA's recommendations now include GLP embryofetal studies in two relevant nonclinical species, with adequate evaluation of toxicokinetics. For NMEs administered by the ocular route, information only regarding the developmental toxicity of metabolites may not be sufficient to characterize the developmental toxicity potential of the administered drug product. In the case of latanoprostene bunod, the potential developmental toxicity of latanoprostene bunod cannot adequately be extrapolated from results for testing the metabolites separately. The Sponsor's proposal (b) (4)

(b) (4)

Available developmental toxicity data for latanoprost acid alone and for 4-hydroxybutyl nitrate alone may be inadequate to predict the interactions of these metabolites with the parent drug and each other. Adequate GLP embryofetal studies in two relevant nonclinical species with latanoprostene bunod will cover the potential interactions of the metabolites in vivo.

Non-Clinical Question 2: Bausch & Lomb confirms that no carcinogenicity, photosafety and development or reproductive toxicity studies specific to latanoprostene bunod (parent compound) were conducted, because: a) the nonclinical data available for (b) (4) active latanoprost (b) (4) (shares the same NO-donating moiety as latanoprostene bunod) demonstrate that latanoprostene bunod is safe for its intended purpose and, b) the very low systemic exposure to the parent compound and metabolites as demonstrated during the clinical pharmacokinetic (PK) study (study 809).

Does the Agency confirm that no carcinogenicity, photosafety, safety pharmacology, and development or reproductive toxicity studies conducted with the parent compound (latanoprostene bunod) are required?

FDA Response:

See the response to Non-clinical question # 1.

Meeting Discussion: None

CLINICAL

Clinical Question 1: Before performing integrated statistical analysis for Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), B&L is planning to revise the currently approved statistical analysis plans (SAP)

Does the Agency concur that these modifications/revisions, when applied after amending the established (approved) SAPs and issuing a new version and thereafter performing pooled analysis accordingly, would not affect the validity and integrity of the ISE and ISE findings and their potential for labeling claims?

FDA Response:

No, we do not recommend excluding randomized and treated subjects from the primary efficacy analysis as this could potentially introduce bias. As discussed during the EOP-2 meeting, we still recommend that the primary efficacy analysis should be conducted on the ITT population which includes all randomized subjects with LOCF used to deal with missing data. For randomized and treated subjects with no IOP measurement, the worst possible outcome from the treatment group they belong to can be imputed.

Additionally, as discussed during the EOP-2 meeting and stated in your current SAP, the analysis should also be conducted on the PP population using observed data only. If the results from the two analyses differ, an explanation and additional analyses are recommended to help identify the reasons for the differences and the impact of potential bias on the results. One such analysis could be the analysis on your proposed "ITT BOL Phase 3 ITT population" with LOCF used to impute missing data.

We also recommend that you perform sensitivity analyses on the ITT population (all randomized subjects) using different missing data methods and provide an explanation in the event that there is any noticeable discrepancy between the results of the sensitivity analyses and the primary efficacy analysis.

Meeting Discussion:

The Division re-iterated that the primary efficacy analysis should be conducted on the ITT population which includes all randomized subjects and agreed with the proposed approach for the imputation of missing data using LOCF. The Division recommended that the analysis of the primary efficacy endpoint also be performed on the per-protocol population as a sensitivity analysis and an explanation provided if the results from the two analyses differ.

The Division recommended including the sensitivity analysis results in a subsection under efficacy analysis and in the Integrated Summary of Efficacy (ISE).

Clinical Question 2: Reference is made to minutes of the meeting held with the Division, on September 26, 2012 during which the two phase 3 primary efficacy studies design and statistical analysis plan (SAP) were discussed.

- a) Does the Agency confirm that the Integrated Summary of Efficacy pooled analysis, as described in the SAP provided in the briefing document for the 3 months efficacy primary endpoints could be supportive of claiming non-inferiority to timolol?**

FDA Response:

No. To determine the adequacy of the study results in supporting the non-inferiority claim, we need to review the efficacy summaries and data for all studies involving the study drug separately in addition to the ISE. To support a non-inferiority claim, at least two trials, each demonstrating non-inferiority of latanoprostene bunod ophthalmic solution to timolol would be expected. See also the response for Clinical question 1.

Meeting Discussion: None

- b) Does the Agency confirm that the pooled analysis, as described in the SAP provided in the briefing document, for the 3 months efficacy primary endpoints could be supportive of claiming superiority to timolol?**

FDA Response:

No. To support a superiority claim, at least two trials, each demonstrating clinically significant superiority between latanoprostene bunod ophthalmic solution and timolol would be expected.

Meeting Discussion:

The Division stated that clinically significant superiority should be demonstrated with a clear benefit to risk ratio. Currently, the Division considers additional 4mmHg to 6mmHg of intraocular pressure (IOP) lowering over the comparator as clinically

significant; all time points measured should show superiority to the desired IOP reduction range.

The Sponsor asked if considerations should be given to target key secondary endpoints such as percent of patients with 25% reduction or achieving ≤ 18 mmHg. The Division responded that it is not aware of data to support that these targets have a clinical benefit on visual function over time.

- c) **Does the Agency confirm that the approach taken to demonstrate IOP reduction in the efficacy phase of the studies could be supportive of claiming that in clinical studies up to 12 weeks in duration, significantly greater proportion of patients with open-angle glaucoma or ocular hypertension and mean baseline pressure of (b) (4) 26 mm Hg, who were treated with latanoprostene bunod once daily in the evening (b) (4)**

FDA Response:

No. To support a superiority claim, at least two trials, each demonstrating clinically significant superiority between latanoprostene bunod ophthalmic solution and timolol would be expected.

Meeting Discussion: None

- d) **Further, does the agency agree that (b) (4) (b) (4) could support that these findings (b) (4) respectively?**

FDA Response: No.

Meeting Discussion: None

- e) **Does the Agency confirm that the approach taken (SAP of the ISE) to demonstrate sustainability of IOP reduction up to 12 months could be supportive of claiming that: << in clinical studies up to 12 months in duration, patients with open-angle glaucoma or ocular hypertension (b) (4) baseline pressure of (b) (4) 26 mmHg (b) (4)**

FDA Response:

Specific labeling is a review issue requiring review of a submitted New Drug Application. We need to review the efficacy summaries and data for all studies involving the study drug separately. In the absence of a concurrent control, very limited data, if any, is expected to be included in the labeling.

Meeting Discussion: None

Clinical Question 3: Reference is made to minutes of the meeting held with the Division, on September 26, 2012 during which the two phase 3 primary efficacy studies design and statistical analysis plan (SAP) was discussed.

- a) **Bausch & Lomb plans to submit an Integrated Summary of Safety analyses as per the SAP presented at section 1.6.2.14.6 Appendix F. The SAP has been designed to conduct two pooled analyses: a first one to support the initial NDA submission and the second one to submit in the safety update. Would the proposed approach meet the requirements for filing, and be supportive of labeling and registration?**

FDA Response:

Yes, but all 12 month data available at the time of submission should be should be submitted in the original application.

Meeting Discussion: None

- b) **We anticipate that at initial NDA submission the provisional safety population data to be submitted will include the safety data of at least 1300 subjects who were exposed to at least one dose of latanoprostene bunod 0.24% QD and of which at least 450 subjects were exposed for 6 months and during at least 120 subjects were exposed during 12 months at cut-off data point of November 24, 2014, thus meeting FDA agreement on September 26, 2014. Would this total safety population data satisfy NDA filing requirement?**

FDA Response:

Yes, we would agree that you would have met a minimum requirement.

Meeting Discussion: None

- c) **We anticipate to complete the total safety population by providing in the 120-days safety update to be submitted during NDA review, the safety data of all remaining subjects having completed 12 months exposure and other additional subjects exposed to at least one dose of latanoprostene bunod QD 0.024% at cut-off data point of June 2015 (when study 769 is completed), thus contributing to the final total safety population.**

Of the final total safety population (approximately 1549 subjects exposed to at least one dose of latanoprostene bunod regardless of dosing regimen and duration), we

expect that approximately 130 subjects will be Japanese subjects exposed at least 6 months, during study 811 (conducted only in Japan) and 141 subjects exposed during a shorter duration (2-4 weeks).

Would this subset of safety data be considered:

- i. reflective and representative of US population**
- ii. be supportive of the total patient safety population to meet ICH requirement of at least 1500 subjects**
- iii. be supportive of the labelling?**

FDA Response:

Applications are expected to be complete at the time of submission. Data submitted after the initial submission may or may not be included in the Agency's first action on the application. Whether the final patient dataset is reflective of the relevant U.S. demographics is a review issue.

Meeting Discussion: None

PRODUCT QUALITY (CHEMISTRY, MANUFACTURING & CONTROLS)

Quality Question 1: Based on the information and arguments presented in section 1.6.12.3 Related Substances in the Drug Product, does the Agency concur with rationale for the calculations of total related substances for the finished drug product?

FDA Response:

Your method of calculating the total related substances for the finished drug product is acceptable. You should include in the NDA drug product stability data that show that the drug substance specified impurities (with the exception of (b) (4) the drug product on stability.

Meeting Discussion: None

Quality Question 2:

- a) Does the Agency concur that the specifications for drug substance and drug product as listed in Table 23 and Table 27 respectively are appropriate to support the filing of the NDA and product registration?**

FDA Response:

The adequacy of the drug substance and drug product specifications is an NDA review issue. However, you appear to be measuring appropriate parameters. You should provide complete justifications in the NDA and in particular you should provide toxicological qualification data for the various impurities and data to support the lower limit of the preservative specification.

- b) Specifically, B&L does not plan to include endotoxin testing in the forthcoming NDA submission. Does the Agency concur with our proposal?**

FDA Response: *Acceptable.*

Meeting Discussion: None

c)

(b) (4) (b) (4)

[Redacted]

Does the Agency agree that we can submit this change as an amendment to the submission during the review period or should this change be submitted in the drug product specification in the initial NDA?

FDA Response:

No. The application is expected to be complete at the time of the submission.

Meeting Discussion:

The Division confirmed that the Sponsor needs to follow the current specification at the time of submission. If the USP <789> is still in place, then this needs to be followed. The Division further noted that USP criteria are the minimum standard, but the Division may require a higher standard.

Quality Question 3: Bausch & Lomb has designed and conducted a stability program which includes long term and accelerated storage conditions to support expiry dating in accordance with ICH guidelines for drug product stored in (b) (4) containers to support the label storage and usage requirements.

a) Based on the outcomes of the investigation described in the briefing document, does the Agency concur that the observed OOS (b) (4) results have been satisfactorily resolved?

FDA Response:

You should submit the complete investigational report with the NDA and describe the steps that you have taken to mitigate the problem. Review of your root cause analysis and the stability data from the drug product batches manufactured using the improved bottles will be particularly important in our evaluation of this issue.

Meeting Discussion: None

b) Since the (b) (4) results are not due to a product related stability issue, does the Agency concur that the affected registration batches can be supportive of filing and product registration?

FDA Response:

We agree that the affected registration batches can be supportive of filing and product registration.

Meeting Discussion: None

- c) **B&L plans to** [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4) **Initial release data from these stability batches will be provided at the time of the NDA submission. Stability data representing 6 months time point will be provided during the review of the NDA in an amendment at about 5 months after submission receipt. Does the Agency concur that the additional data could be submitted as an NDA amendment and will not affect reviewers timelines and PDUFA goal date?**

FDA Response:

The application is expected to be complete at the time of submission. If the additional drug product stability data is critical to the approvability of the application, it is recommended that the data be submitted at the time of the original submission. We recommend that you submit in the initial NDA at least 3 months of stability data for 3 batches of the drug product manufactured [REDACTED] (b) (4). Please note that the expiration dating period will be assigned based on the overall stability data submitted in the application.

Meeting Discussion:

The Sponsor proposed to seek initial approval for the 5mL presentation and stated that at the time of initial NDA submission they would provide 12 months of stability data for 3 batches of 5ml bottles [REDACTED] (b) (4). The Division concurred with this approach.

The Sponsor also proposed [REDACTED] (b) (4)

The Division noted that the 5 mL bottle was expected to last for 60 days and so the antimicrobial preservative effectiveness testing should cover that period. The Sponsor confirmed that the in-use testing for 5ml bottle covers microbial and chemical quality testing.

- d) **In addition to the ICH stability studies, B&L conducted the following studies: photostability, freeze thaw cycling, weight loss through expiry on primary stability batches, in-use testing, leachable/extractables on commercial container closure and droplet volume evaluation from multiple container batches. NDA. Does the Agency concur that these studies will adequately support filing and registration?**

FDA Response:

The adequacy of the studies will be an NDA review decision based on an examination of the actual data. At this stage we have no other studies to suggest.

Meeting Discussion: None

- e) **Specifically for in-use testing, B&L has tested (b) (4) the (b) (4) fill size (5 mL, for approximately 60 days treatment duration) as this represents the worst case scenario for the most dispensing events by the patient. Does the Agency concur that this study will adequately support filing and registration?**

FDA Response:

Your proposal appears reasonable. We will need to review the application to determine whether it will adequately support filing and registration.

Meeting Discussion: None

REGULATORY QUESTIONS

Regulatory Question 1:

B&L plans to submit the NDA in eCTD format, with comprehensive data and summaries to show the safety and effectiveness of latanoprostene bunod for the claimed indication and usage.

- a) **Does the Agency agree that the format and content meet the expectations for filing of the initial NDA?**

FDA Response:

See the previous responses to Clinical questions 1, 2, and 3.

Meeting Discussion: None

- b) **Does the Agency agree that the format and content meet the expectations for filing of the 120-day safety update?**

FDA Response:

Yes, but all 12 month data available at the time of submission should be submitted in the original application.

Meeting Discussion: None

Regulatory Question 2: Bausch & Lomb has established that latanoprostene bunod is a new chemical entity that is rapidly metabolized in situ to latanoprost acid, an FP receptor agonist, and 4-hydroxybutyl nitrate (also referred to as butanediol mononitrate [BDMN]), a nitric oxide (NO)-donating moiety. We consider, based on the totality of scientifically

valid and clinically meaningful nonclinical and clinical data to be submitted in the NDA, that this compound (b) (4)

(b) (4)

(b) (4)
?

FDA Response:

No. (b) (4).
(b) (4), the same class Warnings/Precaution and Dosing recommendations as the prostaglandin analogs will be considered during the review.

Meeting Discussion: None

Regulatory Question 3: Based on the totality of the data available to us, Bausch & Lomb considers that latanoprostene bunod is a new chemical entity presenting no new significant safety issues. The clinical design of the adequate and well-controlled studies include similar endpoints as products developed for the reduction of IOP (glaucoma), and we do not anticipate any controversial issues that would require FDA to consult an advisory committee.

Would the Agency confirm that no advisory committee will be required?

FDA Response:

All new molecular entities are considered for Advisory Committee review unless during review of the application there is a reason for not presenting the application to an Advisory Committee. We expect to make that determination during the review of the application.

The studies submitted appear to provide an evaluation of IOP reduction. These studies do not appear to evaluate the effect of your product on the conditions that led to elevated intraocular pressure (glaucoma). It is recommended that your application distinguish between these two conditions.

Meeting Discussion: None

ADDITIONAL AGENCY COMMENTS

1. Regarding labeling:
 - a. It is preferable to provide exposure multiples based on systemic area under the curve (AUC) data in sections 8 and 13 of the label. If adequate pharmacokinetic/toxicokinetic data are available, please calculate exposure multiples based on systemic AUC data for label sections 8 and 13, and provide the datasets used to make these calculations.

- b. If systemic AUC data is not available, but other estimates of systemic exposure are available, it is recommended that all available data be used to estimate systemic exposure and that the package insert describe the method used to estimate the exposure multiple along with any relevant non-clinical findings. The data and assumptions used to estimate systemic exposure should be submitted.*
- 2. Please be aware of the Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (<https://federalregister.gov/a/2014-28241>), published December 4, 2014, with an effective date of June 30, 2015. Applications submitted on or after June 30, 2015 should comply with this final rule. FDA requests that your labeling be consistent with the rule (even if submitted prior to the effective date). You may find it helpful to refer to the CDER webpage (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>) and to the 2014 Labeling draft guidance, "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry" (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm425398.pdf>)*
- 3. We have the following comments regarding submission of published literature to support your NDA:*
 - a. Published literature relevant to your product should be considered, and relevant data should be summarized in the NDA.*
 - b. The nonclinical summary(ies) are typically organized to address each of the required nonclinical elements (e.g. pharmacology, pharmacokinetics, general and ocular toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.) and if literature is being relied upon to support these requirements, these data should be adequately summarized within the appropriate subsections of the integrated summary ('Nonclinical Written and Tabulated Summaries'). A copy of each cited article should be provided. Please note that review articles cannot be relied upon to support an application; the source articles which contain full study data should be provided or incorporated by reference.*
 - c. Published data is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.*
 - d. Please identify any listed drug(s) described in the submitted published literature [e.g. any trade name(s)].*

POST-MEETING COMMENT:

We note that in PK Study #809, you were able to quantify in human plasma one of the two latanoprostene bunod active moieties, i.e., latanaprost acid but not BDMN (the NO-donating moiety). Thus, in order to quantify the systemic exposure to NO, we recommend that you consider obtaining time-course profiles of the change from baseline in % methemoglobin over 12 hours following single and repeat dosing of latanoprostene bunod ophthalmic solution 0.024% in a subset of patients (n=8 to 12) enrolled in the ongoing Phase 3 trials (e.g., Study #769).

PREA REQUIREMENTS

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.

We refer to your submission dated and received October 2, 2014, containing your Initial Pediatric Study Plan (iPSP), and your submission dated and received December 12, 2014, containing your Agreed iPSP, requesting a waiver for the pediatric population of birth to 17 years old for the proposed indication, reduction of intraocular pressure in patients with open-angle glaucoma. We also refer to our advice/information request letter sent on January 9, 2015, confirming our agreement to your Agreed iPSP.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

We also refer you to the Draft Guidance for Industry-Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Contents and format regarding the Pregnancy and Lactation Labeling Rule (PLLR)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

None

ATTACHMENTS AND HANDOUTS

Sponsor's presentation on follow up questions/comments submitted on February 8, 2015.



(b) (4)

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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/

WILEY A CHAMBERS
03/09/2015



IND 73435

MEETING MINUTES

Bausch and Lomb Incorporated
Attention: Isabelle B. Lefebvre, Bsc, RAC EU & US
Director, Global Branded Rx Portfolio & Regulatory Strategy
7 Giralda Farms, Suite 1001
Madison, New Jersey 07940

Dear Ms. Lefebvre:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BOL-303259-X ((b) (4) [REDACTED]).

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on September 26, 2012.

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

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

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:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time: September 26, 2012, 12:30 pm
Meeting Location: 10903 New Hampshire Avenue
Silver Spring, MD 20903
Building 22, Room 1315

Meeting Type: End of Phase 2

Application: IND 73435
Drug: BOL-303259-X ([REDACTED] (b) (4))

Sponsor: Bausch and Lomb Incorporated
Indication: Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Michael Puglisi

FDA PARTICIPANTS:

Renata Albrecht/ Division Director
Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Martin Nevitt/ Medical Officer
Lori Kotch/ Pharmacology/Toxicology Team Leader
Andrew McDougal/ Pharmacology/Toxicology Reviewer
Gerlie Gieser/ Clinical Pharmacology Reviewer
Abel Eshete/ Statistics Reviewer
Dongliang Zhang/ Statistics Reviewer
Michael Puglisi/ Project Manager

SPONSOR PARTICIPANTS:

Marvin Garrett/ Vice President, Regulatory Affairs
Isabelle Lefebvre/ Director, Regulatory Affairs
Richard D'Souza/ Vice President, Research and Development and Regulatory Affairs
Baldo Sforzolini/ Vice President, Drug Development
Quintus Ngumah/ Director, Clinical Affairs
Mary Richardson/ Executive Director, Preclinical
Jason Vittitow/ Director, Clinical Affairs
[REDACTED] (b) (4) / Clinical Consultant

MEETING OBJECTIVE:

To discuss the nonclinical, clinical, and regulatory development of BOL-303259-X [REDACTED] (b) (4)) for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the August 21, 2012, background package (see bolded text below) were provided to the Sponsor in an email dated September 20, 2012 (see text in italics below). This meeting served to clarify those responses. Discussion during the meeting is reflected in normal font.

Non-Clinical Question 1

Reference is made to the previous meeting held on February 14, 2006 between the Division and Pfizer, the former holder of IND #73435. As previously advised to Pfizer, based directly on the nonclinical testing completed on BOL-303259-X, and indirectly on the extensive data available for latanoprost acid and nitric oxide, Bausch + Lomb proposes not to conduct (additional) carcinogenicity studies, photosafety studies, developmental fertility, or reproductive toxicity studies with BOL-303259-X.

Can the Division reaffirm that the non/preclinical program of completed and planned studies is adequate to support

- a. Phase 3 clinical trials, and;**
- b. Submission of a fileable and reviewable application, and, subject to FDA's review, approval of BOL-303259-X for the proposed indications?**

Agency Response: No. Based on the supporting documentation provided, FDA infers that this question was intended to refer both to the documentation for 2006 meeting and also FDA's pre-meeting responses sent August 13, 2007 for the scheduled August 15, 2007 meeting.

Regarding the Phase 3 trial -

FDA concurs that the nonclinical program of completed/planned studies is adequate to support Phase 3 clinical trials, with two important reservations:

- a. The study report for "In vivo bone marrow micronucleus assay of PF-03187207" (report # 07GR073) was not identified in the IND. This report was listed as "pending" for the July 18, 2007 briefing package. Prior to initiation of a Phase 3 trial, please indicate when the IND the report was submitted, and if it was not previously submitted, please send this report to the IND. Because PF-03187207 was clearly clastogenic when tested in human peripheral lymphocytes in vitro (report # 06AA133), understanding the results of the in vivo micronucleus assay prior to the initiation of the Phase 3 trial is important.*
- b. Review of the file notes that submission of a 3-month monkey study was planned (as per the 7/18/2007 meeting package and FDA's 8/13/2007 response); no such study was identified in the IND, and no discussion of a 3-month monkey study was found in the 8/21/2012 briefing package. Prior to initiation of a Phase 3 trial, clarify whether a 3-month study was initiated. If a 3-month study was initiated, prior to initiation of a Phase 3 trial, either indicate when study summaries and the study report were submitted to the IND or submit these data to the IND.*

Regarding the NDA –

- a. FDA's position, as stated in the August 13, 2007 correspondence, "we do not anticipate*

that additional nonclinical studies will be needed” was based on right-of-reference in IND 73435 to both publically available information and confidential business information held by the previous sponsor (Pfizer) regarding the genotoxicity, carcinogenicity, developmental and reproductive toxicity (DART) of the metabolites 4-hydroxybutyl nitrate and nitric oxide. The briefing package does not indicate whether Bausch and Lomb can or will incorporate the previously-referenced confidential business information in the NDA. Please provide a summary of the data upon which you plan to rely for the NDA’s demonstration of safety for the metabolites (e.g. 4-hydroxybutyl nitrate and nitric oxide) for genotoxicity, carcinogenicity, and DART. For general information regarding CDER’s expectations for the testing of metabolites, please see:

- a. 2008 Guidance for Industry. Safety Testing of Drug Metabolites (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079266.pdf>)
 - b. 2010 Guidance for Industry. M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>)
 - c. 2012 Guidance for Industry. M3(R2) Questions and Answers (<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM292164.pdf>)
- b. Review of the IND file noted that two potentially mutagenic impurities were previously identified: [REDACTED] ^{(b) (4)}. As soon as feasible, but no later than the NDA, provide your basis for concluding that each impurity is safe (e.g. exposures have already been qualified by testing, or exposures are below the threshold for qualification).
- c. DTOP acknowledges receipt on June 2, 2011 of the 9-month topical ocular instillation toxicity and toxicokinetic study with PF-03187207 in cynomolgus monkeys (report # 6348-415), and also your notification in the Annual Report (AR) submitted May 22, 2012 that the study was re-opened to complete additional analyses (mainly histopathology). Although DTOP is awaiting submission of the final revised report, based on your summary in the AR, DTOP has no nonclinical objection to the proposed Phase 3 trial. Submit the final revised report as soon as feasible, but no later than the NDA.

Meeting Comments: Prior to the meeting, in an email dated 9/21/12, the Sponsor clarified that there is no 3-month monkey study report; rather, the 9-month monkey study was conducted and completed. In addition, the revised final report for the micronucleus study was submitted to the IND on June 1, 2011. There was no further discussion of these issues during the meeting.

Clinical Pharmacology Question 1

Does the Agency agree that the existing and proposed clinical pharmacokinetic data are sufficient to support approval of an NDA for the proposed indication?

Agency Response:

Disagree. In the planned clinical pharmacokinetic study (Study 809; PLUTO), we recommend that you attempt to quantify plasma concentrations of BOL-303259-X (the parent drug) and its metabolite 4-hydroxybutyl nitrate (BDMN), in addition to the latanoprost acid metabolite, using

sensitive PK assays and sample processing/storage strategies that would optimize analyte stability. Your proposal to determine the plasma concentrations of analyte after the first dose and the last dose (on day 28) of BOL-303259-X in 15-20 healthy subjects, and the proposed PK sampling timepoints in Study 809 are acceptable. Additional or revised comments may be provided at the time of submission and review of the full study protocol.

Although we do not anticipate the need for additional clinical pharmacology studies, the final determination will be made after reviewing the findings of Study 809.

Meeting Comment: There was no discussion of this matter.

Clinical Question 1

Based on the study synopsis and summary of preliminary data provided in the briefing document, does the FDA agree that the completed Phase 2 study (#659) is adequate to support the proposed dose selection for Phase 3 trials to evaluate the use of BOL-303259-X (latanoprostene bunod) 0.024% QD for the proposed indication?

Agency Response: *Yes.*

Meeting Comment: There was no discussion of this matter.

Clinical Question 2

Bausch + Lomb plans to conduct two pivotal Phase 3 primary efficacy studies, the details of which will be presented in the Briefing document: Study #769, “A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% Ophthalmic Solution With Timolol Maleate Ophthalmic Solution 0.5% in Subjects With Open-Angle Glaucoma or Ocular Hypertension – APOLLO Study”, and Study #770, “A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% Ophthalmic Solution With Timolol Maleate Ophthalmic Solution 0.5% in Subjects With Open-Angle Glaucoma or Ocular Hypertension – LUNAR Study”, to support registration and approval for the proposed indication.

a) Does the agency agree with the proposed Phase 3 trial design, timolol 0.5% (BID) as the comparator, primary and secondary endpoints and statistical analysis plan as summarized in the synopses?

Agency Response: *Yes, but only synopses are provided. When the full protocols and statistical analysis plans are provided, the Agency may have additional comments.*

We have provided some comments for you to consider when you prepare the full protocol and the statistical analysis plan as part of our response to Question #5.

b) Does the Agency agree that the primary statistical model will use an analysis of covariance (ANCOVA) with treatment as a fixed-effect term, and baseline IOP as a covariate to account for the variation in the baseline IOP?

Agency Response: Yes, since an unadjusted analysis will also be performed and submitted as a sensitivity analysis.

- c) **For the primary efficacy endpoint (i.e., IOP), we plan to conduct PP analysis (primary analysis population) and ITT analysis (secondary analysis population). Does the agency agree?**

Agency Response: We recommend 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. Robustness of the data set is generally demonstrated when the respective results corroborate (approximately equal values and equivalent significance). If the results from the two analyses differ, an explanation and additional analyses are recommended to help identify the reasons for the differences and the impact of potential bias on the results.

From a statistical prospective, we don't agree on the use of the PP as the primary analysis population because according to your sample size calculations, this analysis might exclude around 25% of randomized subjects. This consequently might introduce substantial bias in your study results. We recommend the use of the ITT population consisting of all randomized subjects as the main analysis population and the PP population as a secondary analysis population. There should also be a sensitivity analysis together with what assumptions went into the choice of method for handling missing data defined in the protocol or the statistical analysis plan. Other potential sensitivity analyses may include the use of the Worst Observation Carried Forward (WOCF) approach, in which the worst possible outcome in the subject's treatment group is used to impute the missing data. In addition, other methods such as multiple imputations should be considered as additional sensitivity analyses. If there is a noticeable discrepancy in the results, an explanation should be given. When addressing the issue of missing data, we recommend you to consult the book "The Prevention and Treatment of Missing Data in Clinical Trials" (Authored by Panel on Handling Missing Data in Clinical Trials and National Research Council).

- d) (b) (4)

Does the agency agree? Assuming positive data with multiplicity adjustment, could these results be reflected in the label?

Agency Response: Potentially, but labeling is a review issue requiring review of a submitted New Drug Application. (b) (4)


The protocol should clearly specify a testing procedure to control the overall type I error at 0.05 level for two-sided tests for both the primary endpoint and the secondary endpoints.

- e) **Will the FDA accept the use of generic timolol as the active comparator (B+L approved generic timolol ANDA #74776), instead of the branded product (TIMOPTIC[®], NDA #018086)?**

Agency Response: Yes.

- f) **Per 21CFR314.126(a), would the Division agree that the two proposed phase 3 studies (#769 and #770) are adequate and well-controlled investigations and, as such, provide “substantial evidence” of efficacy to support approval of the proposed indication?**

Agency Response: Potentially, but only synopses are provided. When the full protocols and statistical analysis plans are provided, the Agency may have additional comments.

Meeting Discussion: The Sponsor discussed plans to minimize missing data and improve compliance in their Phase 2 studies (769 and 770). The Agency stated that an assumption that there will be a 13% dropout rate is acceptable for the purpose of calculating the sample size, however, a 13 % dropout rate for patients would be unusually high for a 3-month IOP study.

The Agency reiterated its recommendation 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. If the results from the two analyses differ, an explanation and additional analyses are recommended to help identify the reasons for the differences and the impact on the interpretation of the results.

The Sponsor raised the possibility of using a target of a percentage-reduction from baseline for a secondary endpoint. The Agency acknowledged that this issue has been the subject of many discussions and has been attempted in past trials but that a definitive, clinically relevant number has not been determined. The Agency encouraged the Sponsor to collect the information for possible consideration in the future.

The Agency recommended the Sponsor collect data at the 2, 6, and 12 week time points.

(b) (4)

Clinical Question 3

To satisfy the requirements of ICH guidance E1A, “*The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*”, Bausch + Lomb will provide patient population safety data at the proposed selected dose and dosing regimen with two proposed Phase 3 studies (Studies 769 and 770).

Based on the sample size calculation assumptions and a dropout rate of 5% each 3 months, Study #769 and Study #770 will contribute approximately up to 585 subjects exposed to BOL-303259-X for at least 6 months and up to 213 subjects for 12 months. Thus a cohort of at least 300 subjects will be exposed for 6 months and more than 100 exposed for 12 months to BOL-303259-X, QD 0.024%, meeting ICH E1 Section 4 requirements.

- a) **Does the FDA agree that Bausch + Lomb has satisfied the patient safety requirement for the selected dose (BOL-303259-X 0.024% QD) for the label and registration?**

Agency Response: *Provided that a cohort of at least 300 subjects are be exposed for 6 months and more than 100 exposed for 12 months to BOL-303259-X, QD 0.024%, we agree that you will have met a minimum requirement.*

- b) Bausch + Lomb proposes submitting 6 months safety data on at least 472 subjects at the time of NDA submission with a commitment to submit 12 months safety data on 213 patients at the safety update timepoint (4 months safety update as per 21CFR part 314.50(d)(5)(vi)(b)(1) during NDA review. Would the Division agree to this proposal?**

Agency Response: *Yes.*

Meeting Comment: There was no discussion of this matter.

Clinical Question 4

To further evaluate the safety profile of BOL-303259-X during long term, chronic exposure, Bausch + Lomb intends to include an [REDACTED] (b) (4) as safety assessment endpoints at baseline and 12 months of the proposed Phase 3 study #769.

- a) Based on the preliminary information presented in the briefing document, would the Division consider that the design proposed would yield sufficient data to support chronic safety information in the labeling?**

Agency Response: *Potentially; only a synopsis is provided. We will need to review the final protocol for #769. We may have additional comments.*

- b) In the two Phase 3 studies, Study 769 and Study 770, [REDACTED] (b) (4) Does the Agency agree to this approach?**

Agency Response: *Yes. See Agency response to Question 4a.*

Meeting Comment: There was no discussion of this matter.

Clinical Question 5

We will add European sites for the Phase 3 clinical program in support of the NDA.

Would it be acceptable to the Agency if no more than 40% of the patient population comes from these ex-US sites, assuming subject demographics and medical state profiles are representative (or similar to those) of those from US sites?

Agency Response: *Potentially. Patients from relevant U.S. demographic subsets should be studied, including both men and women, different racial/ethnic and eye color groups of clinical interest, and both younger and older patients.*

Meeting Discussion: The Agency reiterated that data from ex-US sites are acceptable as long as the populations studied are reflective of the US population.

Additional Comments:

In order for us to decide the acceptability of the study designs and analyses, we need to review the full protocols, and if possible the statistical analysis plans. However, based on the synopses of the protocols we have the following comments for you to consider. Comments 1-4 correspond to the two phase 3 studies (Study # 769 and 770). Comment 5 is for the phase two study (Study 803), and the last comment is a general comment.

- 1. The primary analyses using ANCOVA with a confidence interval for the least Square means is acceptable. Please provide the sample code you plan to use for the primary analysis in the statistical analysis plan.*
- 2. In the sample size calculation, a 13% dropout rate and a 12% protocol violation rate are assumed. This constitutes 25% of the population. We recommend the inclusion of plans to attempt to minimize missing data and improve compliance.*
- 3. The protocol synopses specify the per-protocol population as the main analysis population. According to your sample size calculations, the PP analysis might exclude around 25% of randomized subjects. This consequently might introduce substantial bias in your study results. We recommend the use of the ITT population consisting of all randomized subjects as the main analysis population and the PP population as a secondary analysis population. There should also be a sensitivity analysis together with what assumptions went into the choice of method for handling missing data defined in the protocol or the statistical analysis plan. Additional sensitivity analyses may include the use of the Worst Observation Carried Forward (WOCF) approach, in which the worst possible outcome in the subject's treatment group is used to impute the missing data. In addition, other methods such as multiple imputations should be considered as additional sensitivity analyses. If there is a noticeable discrepancy in the results, an explanation should be given. When addressing the issue of missing data, we recommend you to consult the book "The Prevention and Treatment of Missing Data in Clinical Trials" (Authored by Panel on Handling Missing Data in Clinical Trials and National Research Council)*
- 4. For study 803 we recommend that you use the ITT population, consisting of all randomized subjects as the main analysis population and include methods to deal with missing data. Please also provide summary statistics for IOP measurement by study time-point, visit and treatment group within each study period.*
- 5. CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:*

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Meeting Discussion: The Agency reiterated its recommendation to use the ITT population for study 803, acknowledging that it is an exploratory study. Because the study is exploratory, the Agency stated that demonstrating statistical significance would not be required.

Regulatory Question 1

Considering the totality of the clinical efficacy and safety data collected during the development program conducted to date and proposed to be conducted during Phase 3 development, if Bausch + Lomb is successful in establishing non-inferiority to timolol 0.5% BID, would the Division approve a label claim of “Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT)”?

Agency Response: *Potentially, but labeling is a review issue requiring review of a submitted New Drug Application.*

Meeting Comment: There was no discussion of this matter.

Regulatory Question 2

Reference is made to the pre-IND meeting held between Pfizer and the Division on February 14, 2006 and to IND sequence 0001, End-of-phase 2 Type B meeting request submitted on June 18, 2012. In connection with that meeting, a waiver for the pediatric population of [REDACTED] (b) (4) was granted for the proposed indications. Can FDA reaffirm this agreement?

Agency Response: *Based on the adverse event profile of the prostaglandin class, these products are not approved for use in the reduction of intraocular pressure in children. The exclusion of subjects Birth – 16 years in your Phase 3 trials is acceptable.*

As part of any eventual NDA package, you will need to submit a full Pediatric Plan for all age groups or a request a formal waiver for all pediatric age groups with your product for a final determination after review by the Division and the Pediatric Review Committee (PeRC).

Meeting Comment: There was no discussion of this matter.

Regulatory Question 3

Bausch + Lomb proposes to submit the original NDA with 6 months Phase 3 safety and efficacy data. The 12 months long term safety data will be filed at 4 months safety update timepoint. Considering the long term safety data is also part of the integrated safety summary (ISS), we would like to confirm with the Division the ability to submit data and the revised ISS:

- a) **At the safety update time point (4 months safety update as per 21CFR part 314.50(d)(5)(vi)(b)(1) during NDA review process?**

Agency Response: Yes, although all 12 month data available at the time of submission should be submitted at the time of original submission.

- b) Would the revised safety data in support of the proposed indications for BOL-303259-X then be included in the labeling?**

Agency Response: Potentially, but labeling is a review issue requiring review of a submitted New Drug Application.

Meeting Comment: There was no discussion of this matter.

ACTION ITEMS: The Agency agreed to issue minutes of this meeting within 30 days.

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/s/

WILEY A CHAMBERS
10/16/2012

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207795

LATE-CYCLE MEETING MINUTES

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated July 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%. We also refer to the Late-Cycle Meeting (LCM) teleconference between representatives of your firm and the FDA on April 8, 2016.

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

If you have any questions, call Lois Almoza, M.S., Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

William M. Boyd, MD
Cross Discipline Team Leader
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: April 8, 2016 from 10:20AM – 11:00AM (EST)
Meeting Format: Teleconference
Application Number: NDA 207795
Product Name: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
Applicant Name: Bausch & Lomb Inc.

Meeting Chair: William M. Boyd, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP (DTOP)
William Boyd, M.D.	Cross Discipline Team Leader (CDTL), DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Jin Chen, M.D.	Acting Associate Director for Labeling, DTOP
Philip Colangelo, Pharm. D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yongheng Zhang, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Mary Lewis, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Derek Smith, Ph.D.	Acting Branch Chief, Office of Pharmaceutical Quality (OPQ)/ Office of Process and Facilities (OPF)/Division of Inspectional Assessment (DIA)
Chunchun Zhang, Ph.D.	Acting Product Quality Team Leader, (OPQ)/Office of New Drug Products (ONDP)
Daniel Schu, Ph.D.	Product Quality Micro Reviewer, OPS/ONDQA
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Abel Eshete, Ph.D.	Statistical Reviewer, OB/DBIV
Michelle Rutledge, Ph.D.	Pharmacist, Office of Surveillance and Epidemiology (OSE)
Roy Blay, Ph.D.	Reviewer, Office of Scientific Investigations
Meena Ramachandra, PhD.	Pharmacist, Office of Prescription Drug Promotion
Diana Willard	Chief Project Management Staff, DTOP
Lois Almoza, M.S.	Regulatory Health Project Manager, DTOP

EASTERN RESEARCH GROUP ATTENDEES

Peggah Khorrami Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Mary Harrell, BsBM	Director Reg. Affairs (RA)
Kwame Obeng, PhD, MSE	Exec. Dir. RA-CMC
Linda Galbier,	Director RA-CMC
Isabelle Lefebvre, MSc.RA	VP RA
Sharon Tonetta, PhD	Head RA
Tage Ramakrishna, MD	Chief Medical Officer, Head of R&D
Jason Vittitow, PhD	Director Clinical
Johnson Varughese	Clinical Operations
Robert Israel, MD	VP Clinical & Medical
Robert Kang	Sr. Director, Data management
Binu Alexander, MD	Sr. Director Clinical
Phil Sturno	VP Development
Saberi Rana Ali, MBBS, MD (Ophth.)	Global Pharmacovigilance/Risk Assessment.
Ezra Lowe, PhD	Sr. Manager Clinical and Non-clin. Pharmacology
Kathleen Krenzer, OD, PhD, DABT	Principal Scientist, Toxicology
Stephen Haight	Vice President of Quality
Yvette Henderson	Director, Labeling , Regulatory Affairs
Nicole Quallis	Manager, Labeling, Regulatory Affairs

BACKGROUND

NDA 207795 was submitted on July 21, 2015 for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

Proposed indication: reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension

PDUFA goal date: July 21, 2016

FDA issued a Background Package in preparation for this meeting on April 4, 2016.

DISCUSSION

1. Introductory Comments

Discussion: After introductions, the Cross Discipline Team Leader (CDTL) stated the ground rules for the teleconference and the objectives of the meeting.

2. Discussion of Substantive Review Issues

Regarding inspections of manufacturing facilities:

During a recent inspection of the Bausch & Lomb, Tampa, Florida, USA, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Discussion: *Bausch & Lomb stated they fully understand the Investigator's concerns* (b) (4)
(b) (4) *They have brought in outside consultants to assist with the process. They also plan to provide monthly updates to the field office and plan to provide three reports prior to the PDUFA goal date of July 21, 2016.*

3. Information Requests

Outstanding information request sent to the Applicant on April 4, 2016.

Discussion: *The Division asked Bausch & Lomb for their timelines for a response to the April 4, 2016. Bausch & Lomb noted they plan on responding to the information request on or around April 28, 2016.*

4. Major labeling issues

Discussion: *The Division plans to provide labeling comments to the Applicant approximately 1 – 2 weeks after receipt of the response to the April 4, 2016, information request. The Division also stated* (b) (4)
(b) (4) *. Bausch & Lomb asked if they should remove the statement from the labeling now, but the Division recommended that Bausch & Lomb wait until they receive the Division's proposed labeling revisions before submitting revised labeling.*

5. Review Plans

We have identified no major safety concerns to date.

There are no Risk Evaluation & Mitigation Strategies (REMS) identified to date for this application beyond routine draft professional labeling for the product.

The PDUFA goal date for this application is July 21, 2016 (Standard NME).

Discussion: *None*

6. Wrap-up and Action Items

1. Bausch & Lomb plans to provide a response to the April 4, 2016 information request on or around April 28, 2016.

2. The Division plans to provide proposed labeling revisions 1-2 weeks after receipt of Bausch & Lomb's response to the April 4, 2016 information request.

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

WILLIAM M BOYD
04/28/2016



NDA 207795

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 8, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: April 8, 2016 from 10:20AM – 11:00AM (EST)
Meeting Location: Teleconference

Application Number: NDA 207795
Product Name: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
Indication: reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension
Sponsor/Applicant Name: Bausch & Lomb Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Regarding inspections of manufacturing facilities: During a recent inspection of the Bausch & Lomb, Tampa, Florida, USA, manufacturing facility for this application, our field investigator

conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes William M. Boyd, M.D. (CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by a discussion.

Regarding inspections of manufacturing facilities:

During a recent inspection of the Bausch & Lomb, Tampa, Florida, USA, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

3. Information Requests

Outstanding information request sent to the Applicant on April 4, 2016.

4. Major labeling issues – 10 minutes

5. Review Plans – 15 minutes

We have identified no major safety concerns to date.

There are no Risk Evaluation & Mitigation Strategies (REMS) identified to date for this application beyond routine draft professional labeling for the product.

The PDUFA goal date for this application is July 21, 2016 (Standard NME).

6. Wrap-up and Action Items – 10 minutes

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/s/

RENATA ALBRECHT
04/04/2016