

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207795Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



Recommendation: **Approval**

**NDA 207795  
Review #3  
Oct 24, 2017**

<b>Drug Name/Dosage Form</b>	Latanoprostene Bunod Ophthalmic Solution
<b>Strength</b>	0.024%
<b>Route of Administration</b>	Topical
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Bausch & Lomb Inc.
<b>US agent, if applicable</b>	NA

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Resubmission of NDA	8/17/2017

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Rohit Tiwari	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang	ONDP/DNDP-I/Branch III
Process	Sung Kim	OPF/DPAIII/PABVII
Microbiology	Daniel Schu	OPF/DMA/MABIII
Facility	Rose Xu	OPF/DIA
Biopharmaceutics	Om Anand	ONDP/DBP/Branch I
Regulatory Business Process Manager	Kristine Leahy	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	6/14/2017	LoA: 7/2014
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/18/2013.	
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/28/2013	
	Type IV		NA		LoA: 6/12/2013	

<sup>1</sup>Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73435	This product during IND development

**2. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		11/13/2015	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

## Executive Summary

### I. Recommendations

Satisfactory information and responses have been submitted to support the quality of biopharmaceuticals aspect; refer to IQA#1 dated 3/25/2016. Quality micro reviewer has recommended approval of this NDA as documented in Addendum #1 to Review #1 dated 4/14/2016. The original NDA was issued a complete response due to the GMP non-compliance of the drug product manufacturing facility (Tampa, Florida).

Drug product, drug substance and process reviewers have recommended approval of this NDA in the resubmission IQA#2, however, the NDA upheld the complete response because the drug product manufacturing facility (Tampa, Florida) had once again resulted in the Office of Process and Facilities recommending Withhold.

As documented in this resubmission, the Office of Process and Facilities has issued an overall recommendation for all facilities on 10/13/2017. Therefore, NDA 207795 is recommended for approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM, for consideration during final labeling.

### II. Summary of Quality Assessments

#### A. Drug Substance [Latanoprostene bunod] Quality Summary

The drug substance is Latanoprostene bunod. Molecular weight is 507.62 and is a Colorless or pale yellow viscous oil. (b) (4)  
(U) (4). The drug substance is referenced in DMF (b) (4) which was found adequate by Dr. Rohit Tiwari on 6/14/2017.

#### B. Drug Product [Latanoprostene Bunod Ophthalmic Solution] Quality Summary

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution in 7.5 mL low density polyethylene (LDPE) bottles with 5 mL fill volume, (b) (4)  
(b) (4) tips and (b) (4) caps.

All components are compendial. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, BAK, impurity, osmolality, pH, particulate matter, weight loss, AET and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 3 batches of drug products in the commercial container closure system at commercial scales (b) (4). All batches complied with the proposed specification.

In this resubmission, thirty-six months of stability data at long term condition (5°C) are updated for three commercial scale registration batches. All the quality attributes remained within the proposed specification. Additionally, the in-use stability data provided in the resubmission support the label storage statement of 25°C for 8 weeks.

1. Strength: Latanoprostene Bunod Ophthalmic Solution, 0.024%
2. Description/Commercial Image: A clear, colorless to slightly yellow, sterile, preserved ophthalmic solution
3. Summary of Product Design: Latanoprostene Bunod Ophthalmic Solution
4. List of Excipients: See review notes, below.
5. Process Selection (Unit Operations Summary)
  - a. Sterilization processes of the drug product, as applicable:  
The subject drug product is a sterile, preserved, topical, ophthalmic solution containing latanoprostene bunod 0.24 mg/mL. The proposed packaging of the drug product includes a 7.5 mL LDPE bottle with a (b) (4) tip and (b) (4) cap. The proposed method of sterilization is (b) (4).  
(b) (4)  
(b) (4) The drug product will be manufactured at the Bausch & Lomb, Inc. Tampa facility (b) (4).  
Data to support the process validation for (b) (4).  
(b) (4)  
(b) (4) The application also included the following studies in support of microbiology product quality sterility assurance: container-closure integrity, preservative effectiveness, and in-use studies. Release and shelf-life specifications of sterile will be supported by sterility and antimicrobial effectiveness testing according to USP<71> and USP<51>, respectively. A Product Quality Microbiology review found the application acceptable.
  - b. Critical equipment: None
6. Container Closure: 7.5 mL low density polyethylene (LDPE) bottles, with (b) (4) tips and (b) (4) caps.
7. Expiration Date & Storage Conditions: 36 months with the storage statement of stored 2°C – 8°C and a cautionary statement, “Protect from light”.
8. List of co-packaged components: None

### C. Manufacturing Process Summary for Drug Product

Manufacturing process for the drug product Latanoprostene Bunod Ophthalmic Solution consists of (b) (4).



(b) (4)

**D. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	VESNEO
<b>Non Proprietary Name of the Drug Product</b>	Latanoprostene bunod ophthalmic solution
<b>Non Proprietary Name of the Drug Substance</b>	latanoprostene bunod
<b>Proposed Indication(s) including Intended Patient Population</b>	For the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension.
<b>Duration of Treatment</b>	NA
<b>Maximum Daily Dose</b>	1 drop/eye/daily
<b>Alternative Methods of Administration</b>	None

**E. Biopharmaceutics Considerations**

Vesneo™ (latanoprostene bunod) 0.024%, is an ophthalmic solution for topical administration. The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation. Since the Applicant has determined the plasma levels of the proposed drug and its metabolites, no biowaiver request has been submitted nor is it required. The pharmacokinetic (PK) studies will be reviewed by the Office of Clinical Pharmacology [OCP]. From the Biopharmaceutics perspective, NDA 207795 for Vesneo™ (latanoprostene bunod ophthalmic solution) 0.024%, is recommended for APPROVAL.

1. BCS Classification:
  - Drug Substance: N/A
  - Drug Product: N/A
  
2. Biowaivers/Biostudies
  - Biowaiver Requests: N/A
  - PK studies: N/A
  - IVIVC: N/A

**F. Novel Approaches** None

**G. Any Special Product Quality Labeling Recommendations** None

**H. Life Cycle Knowledge Information**

I. From Initial Risk Identification			Review		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site<sup>3</sup></li> </ul>	<b>H</b>	Formulation includes a preservative; sterilization has been validated; facilities were currently "Acceptable".	<b>H</b>	Post-approval stability protocol <sup>2</sup> will test sterility.
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	<b>M</b>	This is a topical product and therefore does not require testing for endotoxin.	<b>L</b>	No endotoxin testing required.
Assay (API), stability	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Raw materials</li> </ul>	<b>L</b>	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	<b>L</b>	
Assay (preservative)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	<b>L</b>	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	<b>L</b>	AET performed on routine stability.
Uniformity of Dose (Fill Vol/ Deliverable volume)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	<b>M</b>	7.5 mL natural LDPE bottle with 5 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	<b>L</b>	
Osmolality	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	<b>L</b>	Clinically relevant specification; stability studies show no significant change.	<b>L</b>	
pH	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure<sup>1</sup></li> <li>Process parameters</li> <li>Scale/equipment</li> </ul>	<b>L</b>	Buffered formulation; No trend on stability observed. <span style="background-color: gray; color: gray;">(b) (4)</span>	<b>L</b>	

Particulate matter	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>. <sup>(b) (4)</sup> 	M	
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<sup>1</sup> Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

<sup>2</sup> Post-approval stability protocol provides for testing of all quality attributes.

<sup>3</sup> Facilities were currently “**acceptable**”.

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*Comparability Protocols*

**Reviewer's Assessment: N/A**

*Post-Approval Commitments (For NDA only)*

**Reviewer's Assessment: N/A**

*Lifecycle Management Considerations*

**Expedited post-approval inspection of Bausch & Lomb is recommended to verify corrections to the previous PAI/CGMP inspection.**

*List of Deficiencies: None*

*Primary Facilities Reviewer Name and Date:*

*Rose Xu, Facility Reviewer, 10/10/2017*

*Secondary Reviewer Name and Date:*

*Derek S. Smith, Ph.D., 10/13/2017*



Ruo (Rose)  
Xu

Digitally signed by Ruo (Rose) Xu  
Date: 10/13/2017 09:35:22AM  
GUID: 5277e72900088dc65127c01f0d78be60



Derek  
Smith

Digitally signed by Derek Smith  
Date: 10/13/2017 10:25:14AM  
GUID: 508da7480002bfe5d5fe14a12da3599d



Chunchun  
Zhang

Digitally signed by Chunchun Zhang

Date: 10/24/2017 09:45:10AM

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**Recommendation: Complete Response**

**NDA 207795  
Review #2  
July 31, 2017**

<b>Drug Name/Dosage Form</b>	Latanoprostene Bunod Ophthalmic Solution
<b>Strength</b>	0.024%
<b>Route of Administration</b>	Topical
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Bausch & Lomb Inc.
<b>US agent, if applicable</b>	NA

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Resubmission of NDA	2/24/2017
Amendment	4/19/2017

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Rohit Tiwari	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang	ONDP/DNDP-I/Branch III
Process	Sung Kim	OPF/DPAIII/PABVII
Microbiology	Daniel Schu	OPF/DMA/MABIII
Facility	Rose Xu	OPF/DIA
Biopharmaceutics	Om Anand	ONDP/DBP/Branch I
Regulatory Business Process Manager	Kristine Leahy	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP



### Quality Review Data Sheet

#### 1. RELATED/SUPPORTING DOCUMENTS:

##### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	6/14/2017	LoA: 7/2014
	Type IV			NA		LoA: 4/8/2015
	Type IV			NA		LoA: 6/18/2013.
	Type IV			NA		LoA: 4/8/2015
	Type IV			NA		LoA: 6/28/2013
	Type IV			NA		LoA: 6/12/2013

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

##### B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73435	This product during IND development

#### 2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		11/13/2015	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

## Executive Summary

### I. Recommendations

Satisfactory information and responses have been submitted to support the quality of biopharmaceuticals aspect; refer to IQA#1 dated 3/25/2016. Quality micro reviewer has recommended approval of this NDA as documented in Addendum #1 to Review #1 dated 4/14/2016. The original NDA was issued a complete response due to the GMP non-compliance of the drug product manufacturing facility (Tampa, Florida).

As documented in this resubmission, all drug product issues have been satisfactorily resolved; drug substance and process Review #1 recommended Approval and Review #2 upholds the approval recommendations after evaluating this resubmission.

However, the outcome of the most recent inspection of the drug product manufacturing facility (Tampa, Florida) has once again resulted in the Office of Process and Facilities recommending Withhold. Therefore, NDA 207795 is recommended for Complete Response from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM, for consideration during final labeling.

#### A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues--as described above.

2. Action letter language, related to critical issues such as expiration date

The following statement about the unacceptable manufacturing facility (Tampa, Florida) should be included in the CR letter:

*During a recent inspection of the Bausch & Lomb Inc (FEI#1000113778) 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. Benefit/Risk Considerations

NA for CR

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable None

### II. Summary of Quality Assessments

#### A. Drug Substance [Latanoprostene bunod] Quality Summary

The drug substance is Latanoprostene bunod, a new molecular entity. Molecular weight is 507.62 and is a Colorless or pale yellow viscous oil. (b) (4)

(b) (4) The drug substance is referenced in DMF (b) (4) which was found adequate by Dr. Rohit Tiwari on 6/14/2017. (b) (4)

**B. Drug Product [Latanoprostene Bunod Ophthalmic Solution] Quality**

**Summary**

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution in 7.5 mL low density polyethylene (LDPE) bottles with 5 mL fill volume, (b) (4) (b) (4) tips and (b) (4) caps.

All components are compendial. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, BAK, impurity, osmolality, pH, particulate matter, weight loss, AET and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 3 batches of drug products in the commercial container closure system at commercial scales (b) (4) All batches complied with the proposed specification.

In this resubmission, thirty-six months of stability data at long term condition (5°C) are updated for three commercial scale registration batches. All the quality attributes remained within the proposed specification. Additionally, the in-use stability data provided in the resubmission support the label storage statement of 25°C for 8 weeks.

1. **Strength:** Latanoprostene Bunod Ophthalmic Solution, 0.024%
2. **Description/Commercial Image:** A clear, colorless to slightly yellow, sterile, preserved ophthalmic solution
3. **Summary of Product Design:** Latanoprostene Bunod Ophthalmic Solution
4. **List of Excipients:** See review notes, below.
5. **Process Selection (Unit Operations Summary)**

a. **Sterilization processes of the drug product, as applicable:**

The subject drug product is a sterile, preserved, topical, ophthalmic solution containing latanoprostene bunod 0.24 mg/mL. The proposed packaging of the drug product includes a 7.5 mL LDPE bottle with a (b) (4) tip and (b) (4) cap. The proposed method of sterilization is (b) (4)

(b) (4) The drug product will be manufactured at the Bausch & Lomb, Inc. Tampa facility (b) (4). Data to support the process validation for (b) (4)

(b) (4) The application also included the following studies in support of microbiology product quality sterility assurance: container-closure integrity, preservative effectiveness, and in-use studies. Release and shelf-life specifications of sterile will be supported by sterility and antimicrobial effectiveness testing according



## QUALITY ASSESSMENT



to USP<71> and USP<51>, respectively. A Product Quality Microbiology review found the application acceptable.

b. Critical equipment: None

6. **Container Closure:** 7.5 mL low density polyethylene (LDPE) bottles, with (b) (4) tips and (b) (4) caps.
7. **Expiration Date & Storage Conditions:** 36 months with the storage statement of stored 2°C – 8°C and a cautionary statement, “Protect from light”.
8. **List of co-packaged components:** None

### C. Manufacturing Process Summary for Drug Product

Manufacturing process for the drug product Latanoprostene Bunod Ophthalmic Solution consists of (b) (4)



### D. Summary of Drug Product Intended Use

<b>Proprietary Name of the Drug Product</b>	VESNEO
<b>Non Proprietary Name of the Drug Product</b>	Latanoprostene bunod ophthalmic solution
<b>Non Proprietary Name of the Drug Substance</b>	latanoprostene bunod
<b>Proposed Indication(s) including Intended Patient Population</b>	For the reduction of intraocular pressure in patients with openangle glaucoma or ocular hypertension.
<b>Duration of Treatment</b>	NA
<b>Maximum Daily Dose</b>	1 drop/eye/daily
<b>Alternative Methods of Administration</b>	None

### E. Biopharmaceutics Considerations

Vesneo™ (latanoprostene bunod) 0.024%, is an ophthalmic solution for topical administration. The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation. Since the Applicant has determined the plasma levels of the proposed drug and its metabolites, no biowaiver request has been submitted nor is it required. The pharmacokinetic (PK) studies will be reviewed by the Office of Clinical Pharmacology [OCP]. From the Biopharmaceutics perspective, NDA 207795 for Vesneo™

(latanoprostene bunod ophthalmic solution) 0.024%, is recommended for APPROVAL.

1. BCS Classification:
  - Drug Substance: N/A
  - Drug Product: N/A
  
2. Biowaivers/Biostudies
  - Biowaiver Requests: N/A
  - PK studies: N/A
  - IVIVC: N/A

**F. Novel Approaches None**

**G. Any Special Product Quality Labeling Recommendations None**

**H. Life Cycle Knowledge Information**

I. From Initial Risk Identification			Revie		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site<sup>3</sup></li> </ul>	<b>H</b>	Formulation includes a preservative; sterilization has been validated; facilities were currently "Withhold".	<b>H</b>	Post-approval stability protocol <sup>2</sup> will test sterility.
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	This is a topical product and therefore does not require testing for endotoxin.	<b>L</b>	No endotoxin testing required.
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Raw materials</li> </ul>	<b>L</b>	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	<b>L</b>	
Assay (preservative)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	<b>L</b>	AET performed on routine stability.

Uniformity of Dose (Fill Vol/ Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	M	7.5 mL natural LDPE bottle with 5 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	L	
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	Clinically relevant specification; stability studies show no significant change.	L	
pH	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	Buffered formulation; No trend on stability observed. (b) (4)	L	
Particulate matter	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>. (b) (4)	M	

<sup>1</sup> Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

<sup>2</sup> Post-approval stability protocol provides for testing of all quality attributes.

<sup>3</sup> Facilities were currently "withhold".



## **Primary Quality Review**

### **ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION**

Adequate. Refer to Review #1 dated on 3/25/2016.

### **ASSESSMENT OF MICROBIOLOGY**

Adequate. Refer to Addendum #1 to Review #1 dated on 4/14/2016.

### **ASSESSMENT OF ENVIRONMENTAL ANALYSIS**

Adequate. Refer to Review #1 dated on 3/25/2016.

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Recommendation: **Complete Response**

## NDA 207795 Addendum #1 to Review # 1

<b>Drug Name/Dosage Form</b>	Latanoprostene Bunod Ophthalmic Solution
<b>Strength</b>	0.024%
<b>Route of Administration</b>	Topical
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Bausch & Lomb Inc.
<b>US agent, if applicable</b>	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	21-Jul-2015
Amendment	29-Sep-2015
Amendment	05-Oct-2015
Amendment	23-Dec-2015
Amendment	18-Feb-2016
Amendment	11-Mar-2016
Amendment	15-Mar-2016
Amendment	23-Mar-2016

### Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gaetan Ladouceur, Ph. D.	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Process	Sung Kim, Ph. D.	OPF/DP/III/PABVII
Microbiology	Daniel Schu, Ph. D.	OPF/DMA/MABIII
Facility	Denise DiGiulio	OPF/DIA2
Biopharmaceutics	Om Anand, Ph.D.	ONDP/DBP/Branch I
Regulatory Business Process Manager	Erin Andrews, Pharm D	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

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## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	3/18/2016	LoA: 7/2015; Reviewed by Li Mu.
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/18/2013.	
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/28/2013	
	Type IV		NA		LoA: 6/12/2013	

Adequate, Ade Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73435	This product during IND development

**2. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		11/13/2015	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

## Executive Summary

### I. Recommendations

Drug substance, process and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1. As documented in this Addendum, all microbiological issues have been satisfactorily resolved. However, the drug product in-use stability data does not support the label storage statement (b) (4). Specifically, investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies has not been adequately addressed. Furthermore, there appears to be some discrepancy in explaining the OOS issue in the amendment submitted to the NDA as compared to what was observed during the recent inspection (as documented in the FDA 483 issued). Therefore, the NDA is deficient from the drug product perspective.

The outcome of the most recent inspection of the drug product manufacturing facility has resulted in Office of Process and Facilities recommending withhold. Therefore, NDA 207-795 is recommended for **Complete Response** from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

### A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues-- as described above.
2. Action letter language, related to critical issues such as expiration date  
The following statement about the unacceptable manufacturing facility (Tampa, Florida) should be included in the CR letter:  
*During a recent inspection of the Bausch & Lomb Inc (FEI 1000113778) 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.*

The following comment on the in-use stability should also be included:  
*The in-use stability data does not support the label storage statement of (b) (4). There is no scientific justification provided to address the observed (b) (4) issue. Furthermore, we are aware of, from the recent inspection of the Bausch and Lomb facility, of additional investigations into the (b) (4) issue which may present safety concerns (b) (4). A definitive root cause for the (b) (4) stability failures has not been determined.*

*In your resubmission, we recommend that you include the protocol for the in-use stability 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 replace 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)).*

3. Benefit/Risk Considerations: Not applicable for CR

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable** None

## II. Summary of Quality Assessments

### A. Drug Substance [USAN Name] Quality Summary

The drug substance is Latanoprostene bunod, a new molecular entity. Molecular weight is 507.62 and is a colorless or pale yellow viscous oil.

(b) (4)



### B. Drug Product [Established Name] Quality Summary

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution in 7.5 mL low

density polyethylene (LDPE) bottles with 5 mL fill volume, (b) (4)  
(b) (4) tips and (b) (4) caps.

All components are compendial. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, BAK, impurity, osmolality, pH, particulate matter, weight loss, AET and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved. Batch analyses are provided for 3 batches of drug products in the commercial container closure system at commercial scales (b) (4). All batches complied with the proposed specification.

Twenty-four months of stability data at long term condition (5°C) and 6 months data at accelerated condition (25°C/40RH) are provided for three commercial scale registration batches. Impurities including (b) (4) and individual impurities showed (b) (4) but remained within the proposed specification. These results which included statistical analysis supports both the expiration dating period and storage statement listed below. However, the in-use stability data provided does not support the label storage statement (b) (4). Specifically, investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies has not been discussed. Furthermore, there appears to be some discrepancy in explaining the OOS issue in the amendment as compared to what the field investigators observed during the recent inspection (as documented in the 483 issued). Therefore, the NDA is deficient.

1. Strength: Latanoprostene Bunod Ophthalmic Solution, 0.024%
2. Description/Commercial Image: A clear, colorless to slightly yellow, sterile, preserved ophthalmic solution
3. Summary of Product Design: Latanoprostene Bunod Ophthalmic Solution
4. List of Excipients: See review notes, below.
5. Process Selection (Unit Operations Summary)
  - a. Sterilization processes of the drug product, as applicable:

The subject drug product is a sterile, preserved, topical, ophthalmic solution containing latanoprostene bunod 0.24 mg/mL. The proposed packaging of the drug product includes a 7.5 mL LDPE bottle with (b) (4) tip and (b) (4) (b) (4) cap. The proposed method of sterilization is (b) (4)

(b) (4) The drug product will be manufactured at the Bausch & Lomb, Inc. Tampa facility (b) (4) (b) (4). Data to support the process validation (b) (4)

(b) (4) The application also included the following studies in support of microbiology product quality sterility

assurance: container-closure integrity, preservative effectiveness, and in-use studies. Release and shelf-life specifications of sterile will be supported by sterility and antimicrobial effectiveness testing according to USP<71> and USP<51>, respectively. Product Quality Microbiology recommends approval.

b. Critical equipment: None

6. Container Closure: 7.5 mL low density polyethylene (LDPE) bottles, with (b) (4) tips and (b) (4) caps.
7. Expiration Date & Storage Conditions: (b) (4) months with the storage statement of stored 2°C – 8°C and a cautionary statement, “protect from light and freezing”.
8. List of co-packaged components: None

**C. Manufacturing Process Summary for Drug Product**

Manufacturing process for the drug product Latanoprostene Bunod Ophthalmic Solution consists of

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

**D. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	VESNEO
<b>Non Proprietary Name of the Drug Product</b>	Latanoprostene bunod ophthalmic solution
<b>Non Proprietary Name of the Drug Substance</b>	latanoprostene bunod
<b>Proposed Indication(s) including Intended Patient Population</b>	For the reduction of intraocular pressure in patients with openangle glaucoma or ocular hypertension.
<b>Duration of Treatment</b>	NA
<b>Maximum Daily Dose</b>	1 drop/eye/daily
<b>Alternative Methods of Administration</b>	None

**E. Biopharmaceutics Considerations**

Vesneo™ (latanoprostene bunod) 0.024%, is an ophthalmic solution for topical administration. The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation. Since the Applicant has determined the plasma levels of the proposed drug and its metabolites, no biowaiver request has been submitted nor is it required. The pharmacokinetic (PK) studies will be reviewed by the Office of Clinical Pharmacology [OCP]. From the Biopharmaceutics perspective, NDA 207795 for Vesneo™

(latanoprostene bunod ophthalmic solution) 0.024%, is recommended for APPROVAL.

1. BCS Classification:
  - Drug Substance: N/A
  - Drug Product: N/A
  
2. Biowaivers/Biostudies
  - Biowaiver Requests: N/A
  - PK studies: N/A
  - IVIVC: N/A

**F. Novel Approaches** None

**G. Any Special Product Quality Labeling Recommendations** None

**H. Life Cycle Knowledge Information**

I. From Initial Risk Identification			Review		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site<sup>3</sup></li> </ul>	<b>H</b>	Formulation includes a preservative; sterilization has been validated; facilities were currently "Withhold".	<b>H</b>	Post-approval stability protocol <sup>2</sup> will test sterility.
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	This is a topical product and therefore does not require testing for endotoxin.	<b>L</b>	No endotoxin testing required.
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Raw materials</li> </ul>	<b>L</b>	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	<b>L</b>	
Assay (preservative)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	<b>L</b>	AET performed on routine stability.

Uniformity of Dose (Fill Vol/ Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	7.5 mL natural LDPE bottle with 5 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	<b>L</b>	
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Clinically relevant specification; stability studies show no significant change.	<b>L</b>	
pH	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Buffered formulation; No trend on stability observed. (b) (4)	<b>L</b>	
Particulate matter	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>. (b) (4)	<b>M</b>	

<sup>1</sup> Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

<sup>2</sup> Post-approval stability protocol provides for testing of all quality attributes.

<sup>3</sup> Facilities were currently **“withhold”**.

### OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

**Application Technical Lead Signature:**

NDA 207-795 is recommended for **Complete Response** based on OPF (for facilities) and ONDP (OOS for (b) (4) which is linked with the facility issue) evaluation.

**Chunchun Zhang, Ph.D.; Acting CMC Lead, Branch 3, Division of New Drug Products I**

Digitally signed by Chunchun Zhang -S  
 cn=Chunchun Zhang -S, o=9.2342.19200300.100.1.1=2001178137  
 Date: 2016.04.14 20:11:48 -04'00'

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## ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Recommended for approval, see Review #1.

### ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

### Product Quality Microbiology Assessment

#### 1. REVIEW OF COMMON TECHNICAL DOCUMENT- QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

##### S DRUG SUBSTANCE

The drug substance manufacturing process is not the subject of this product quality microbiology review as the drug product is (b) (4) during the drug product manufacturing process.

##### P DRUG PRODUCT

###### P.1 Description of the Composition of the Drug Product

- **Description of drug product**

The drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution that is packaged in low density polyethylene (LDPE) bottles, with (b) (4) (b) (4) tips and (b) (4) caps. Each unit is filled with 5 mL of the sterile solution at a concentration of 0.24 mg/mL.

- **Drug product composition**

The proposed drug product composition is provided in Table 3.2.P.1-1 of the subject submission, which has been reproduced below:

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Latanoprostene bunod <sup>a</sup>	In-house	Active	0.24
Benzalkonium chloride (BAK), (b) (4)	NF	(b) (4) Preservative	(b) (4) b
Polysorbate 80 (b) (4)	NF	(b) (4)	(b) (4)
Edetate disodium (b) (4)	USP	(b) (4)	(b) (4)
Sodium citrate (b) (4)	USP	Buffering agent	(b) (4)
Citric acid, (b) (4)	USP	Buffering agent	(b) (4)
Glycerin (b) (4)	USP	(b) (4)	(b) (4)
Water (b) (4)	USP	(b) (4)	(b) (4)

a This ingredient is (b) (4)

b This amount is equivalent to 0.20 mg/mL BAK in the final formulation.

NF = National Formulary

USP = United States Pharmacopeia



(b) (4)

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### 2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Applicant's Response:** This information was provided under question #3 above.

**Reviewer's Assessment: Adequate**

The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

## A APPENDICES

### A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

**Applicant's Response:** N/A

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:** N/A

### **OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:**

The Division of Microbiology Assessment has reviewed NDA 207795 for Vesneo™ (latanoprostene bunod), and found the microbiology information adequate. From a microbiology perspective, NDA 207795 is recommended for **APPROVAL**.

**Daniel J. Schu, Ph.D.**

**Microbiology Reviewer**

**OPQ/OPF/Division of Microbiology Assessment/Branch 3**

**Secondary Review Comments and Concurrence:**

I concur with the microbiology assessment. NDA 207795 is recommended for **APPROVAL**.

**Jessica G. Cole, Ph.D.**

**Microbiology Quality Assessment Lead (Acting)**

**OPQ/OPF/Division of Microbiology Assessment/Branch 3**



Recommendation: Pending Recommendation

# NDA 207795 Review 1

<b>Drug Name/Dosage Form</b>	Latanoprostene Bunod Ophthalmic Solution
<b>Strength</b>	0.024%
<b>Route of Administration</b>	Topical
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Bausch & Lomb Inc.
<b>US agent, if applicable</b>	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	21-Jul-2015
Amendment	29-Sep-2015
Amendment	05-Oct-2015
Amendment	23-Dec-2015
Amendment	18-Feb-2016
Amendment	11-Mar-2016
Amendment	15-Mar-2016
Amendment	23-Mar-2016

### Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gaetan Ladouceur, Ph. D.	ONDP/DNDAPI/NDBI
Drug Product	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Process	Sung Kim, Ph. D.	OPF/DP/III/PABVII
Microbiology	Daniel Schu, Ph. D.	OPF/DMA/MABIII
Facility	Denise DiGiulio	OPF/DIA2
Biopharmaceutics	Om Anand, Ph.D.	ONDP/DBP/Branch I
Regulatory Business Process Manager	Erin Andrews, Pharm D	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

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## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	3/18/2016	LoA: 7/2015; Reviewed by Li Mu.
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/18/2013.	
	Type IV		NA		LoA: 4/8/2015	
	Type IV		NA		LoA: 6/28/2013	
	Type IV		NA		LoA: 6/12/2013	

<sup>1</sup>Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73435	This product during IND development

**2. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		11/13/2015	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

## Executive Summary

### I. Recommendations

Satisfactory information and responses have been submitted to support the quality of the drug substance and manufacturing process aspects. The composition, and specifications for the drug product are appropriate and the expiration dating period of (b) (4) months is supported by adequate data. However, the in-use stability data provided does not support the label storage statement (b) (4).

Specifically, investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies has not been adequately addressed. Furthermore, there appears to be some discrepancy in explaining the OOS issue in the amendment submitted to the NDA as compared to what was observed during the recent inspection (as documented in the FDA 483 issued).

A final assessment of the manufacturing facilities, micro and drug product is pending at this time. Once the assessments become available, the final recommendation from OPQ will be documented in an addendum.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

#### A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues--
2. Action letter language, related to critical issues such as expiration date  
This will be addressed in the addendum.
3. Benefit/Risk Considerations

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable None

### II. Summary of Quality Assessments

#### A. Drug Substance [USAN Name] Quality Summary

The drug substance is Latanoprostene bunod, a new molecular entity. Molecular weight is 507.62 and is a colorless or pale yellow viscous oil.

(b) (4)

## B. Drug Product [Established Name] Quality Summary

Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution in 7.5 mL low density polyethylene (LDPE) bottles with 5 mL fill volume, (b) (4) (b) (4) tips and (b) (4) caps.

All components are compendial. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, BAK, impurity, osmolality, pH, particulate matter, weight loss, AET and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved. Batch analyses are provided for 3 batches of drug products in the commercial container closure system at commercial scales (b) (4). All batches complied with the proposed specification.

Twenty-four months of stability data at long term condition (5°C) and 6 months data at accelerated condition (25°C/40RH) are provided for three commercial scale registration batches. Impurities including (b) (4) and individual impurities showed (b) (4) but remained within the proposed specification. These results which included statistical analysis supports both the expiration dating period and storage statement listed below. However, the in-use stability data provided does not support the label storage statement (b) (4) (b) (4). Specifically, investigation to determine the root cause for the observed out-of-specification for (b) (4) during in-use stability studies has not been discussed. Furthermore, there appears to be some discrepancy in explaining the OOS issue in the amendment as compared to what the field investigators observed during the recent inspection (as documented in the 483 issued).



<b>Proprietary Name of the Drug Product</b>	VESNEO
<b>Non Proprietary Name of the Drug Product</b>	Latanoprostene bunod ophthalmic solution
<b>Non Proprietary Name of the Drug Substance</b>	latanoprostene bunod
<b>Proposed Indication(s) including Intended Patient Population</b>	For the reduction of intraocular pressure in patients with openangle glaucoma or ocular hypertension.
<b>Duration of Treatment</b>	NA
<b>Maximum Daily Dose</b>	1 drop/eye/daily
<b>Alternative Methods of Administration</b>	None

**E. Biopharmaceutics Considerations**

Vesneo™ (latanoprostene bunod) 0.024%, is an ophthalmic solution for topical administration. The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation. Since the Applicant has determined the plasma levels of the proposed drug and its metabolites, no biowaiver request has been submitted nor is it required. The pharmacokinetic (PK) studies will be reviewed by the Office of Clinical Pharmacology [OCP]. From the Biopharmaceutics perspective, NDA 207795 for Vesneo™ (latanoprostene bunod ophthalmic solution) 0.024%, is recommended for APPROVAL.

1. BCS Classification:
  - Drug Substance: N/A
  - Drug Product: N/A
  
2. Biowaivers/Biostudies
  - Biowaiver Requests: N/A
  - PK studies: N/A
  - IVIVC: N/A

**F. Novel Approaches None**

**G. Any Special Product Quality Labeling Recommendations None**

**H. Life Cycle Knowledge Information**

I. From Initial Risk Identification			Review		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments

Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site<sup>3</sup></li> </ul>	<b>H</b>	Formulation includes a preservative; sterilization has been validated; facilities were currently “ <b>pending</b> ”.	<b>H</b>	Post-approval stability protocol <sup>2</sup> will test sterility.
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	This is a topical product and therefore does not require testing for endotoxin.	<b>L</b>	No endotoxin testing required.
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Raw materials</li> </ul>	<b>L</b>	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	<b>L</b>	
Assay (preservative)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	<b>L</b>	AET performed on routine stability.
Uniformity of Dose (Fill Vol/ Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	7.5 mL natural LDPE bottle with 5 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	<b>L</b>	
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Clinically relevant specification; stability studies show no significant change.	<b>L</b>	
pH	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>L</b>	Buffered formulation; No trend on stability observed. (b) (4)	<b>L</b>	
Particulate matter	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure<sup>1</sup></li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<b>M</b>	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>. (b) (4)	<b>M</b>	

<sup>1</sup> Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

<sup>2</sup> Post-approval stability protocol provides for testing of all quality attributes.

<sup>3</sup> Facilities were currently “**pending**”.

## OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

### Application Technical Lead Signature:

**A final assessment on the status of the facilities from OPF and recommendations from Micro and drug product are pending at this time. When the assessments are available, an overall recommendation from OPQ will be documented in an Addendum.**

Chunchun Zhang, Ph.D., Reviewer Chemist, Branch 3, Division of New Drug Products I

Digitally signed by Chunchun Zhang -S  
United States Government, cn=Chunchun Zhang -S, o=FDA, c=US, email=chunchun.zhang@fda.hhs.gov, ou=CDER, ou=Branch 3, ou=Division of New Drug Products I  
Date: 2016.03.25 15:53:03 -04'00'

## ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Latanoprostene bunod [LBN] is a novel nitric oxide (NO)-donating prostaglandin F2-alpha receptor agonist recommended for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The Applicant described Latanoprostene bunod as an oil at refrigerated and room temperatures, which is practically insoluble in water.

The drug product, Vesneo™ (latanoprostene bunod) 0.024%, is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution containing 0.024% latanoprostene bunod for topical administration. The drug is (b) (4) (b) (4) with a preservative (b) (4) benzalkonium chloride. The Applicant stated that the drug product, with a target pH of 5.5, is formulated to target the physiological pH of the tear fluids which are neutral and close to pH 7.

1. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?**

N/A. Vesneo™ (latanoprostene bunod) 0.024%, is an ophthalmic solution therefore, in vitro dissolution testing is not required.

2. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation<sup>1</sup> presented below in Table 39.1.

**Table 39.1 Qualitative and quantitative composition of the proposed Latanoprostene Bunod Ophthalmic Solution, 0.024%**

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<sup>1</sup> Table 3.2.P.2.2–9 in Original submission

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Latanoprostene bunod <sup>a</sup>	In-house	Active	0.24
Benzalkonium chloride (BAK), (b) (4)	NF	(b) (4) Preservative	(b) (4)
Polysorbate 80 (b) (4)	NF	(b) (4)	(b) (4)
Edetate disodium (b) (4)	USP		
Sodium citrate (b) (4)	USP	Buffering agent	(b) (4)
Citric acid, (b) (4)	USP	Buffering agent	
Glycerin	USP	(b) (4)	(b) (4)
Water (b) (4)	USP		

a This ingredient is (b) (4)  
 b This amount is equivalent to 0.20 mg/mL BAK in the final formulation.  
 NF = National Formulary  
 USP = United States Pharmacopeia

The Applicant submitted two Phase 1 studies (Studies 849 and 809) conducted in healthy subjects to assess the systemic absorption of LBN, Latanoprost Acid [LA], and butanediol mononitrate [BDMN] after single and repeated administration of LBN ophthalmic solution 0.024%. In both studies [849<sup>2</sup> and 809<sup>3</sup>], after repeated QD dosing with LBN ophthalmic solution 0.024%, no quantifiable concentrations of latanoprostene bunod were measured in any collected plasma samples (lower limit of quantitation [LLOQ] of 10 pg/mL). Systemic levels of BDMN were primarily below the limit of quantitation (BLQ) after single and repeated bilateral topical ocular administration of latanoprostene bunod ophthalmic solution 0.024% in humans. Low but quantifiable concentrations of the active metabolite latanoprost acid were observed after single and repeated bilateral dosing of LBN ophthalmic solution 0.024%. The highest observed concentration of latanoprost acid in any collected sample from both Phase 1 studies was 459 pg/mL. Latanoprost acid was rapidly absorbed and rapidly eliminated in humans after ocular administration of LBN ophthalmic solution 0.024%.

These PK studies will be reviewed by the OCP Reviewer. Since the Applicant has determined the plasma levels of the proposed drug and its metabolites, no biowaiver request has been submitted nor is it required.

<sup>2</sup> LBN ophthalmic solution 0.024% was instilled QD in both eyes for 14 days (Study 849) in a healthy Japanese population [male only].

<sup>3</sup> LBN ophthalmic solution 0.024% was instilled QD in both eyes for 28 days (Study 809) in a healthy US-based population [male and female].

## OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

### **Reviewer's Assessment and Signature:**

From the Biopharmaceutics perspective, NDA 207795 for Vesneo™ (latanoprostene bunod ophthalmic solution) 0.024%, is recommended for **APPROVAL**.

**02/11/2016**

Om Anand, Ph.D.  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

### **Secondary Review Concurrence and Signature:**

I concur with Dr. Anand's assessment and recommendation.

**2/11/2016**

Elsbeth Chikhale, Ph.D.  
Acting Biopharmaceutics Lead  
Division of Biopharmaceutics  
Office of New Drug Products, OPQ.

## ASSESSMENT OF MICROBIOLOGY

3. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

The microbiology review is pending as of 24 March 2016.

### Applicant's Response:

#### Reviewer's Assessment:

#### Product Quality Microbiology Assessment

### 1. REVIEW OF COMMON TECHNICAL DOCUMENT- QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

#### S DRUG SUBSTANCE

The drug substance manufacturing process is not the subject of this product quality microbiology review as the drug product is (b) (4) during the drug product manufacturing process.

#### P DRUG PRODUCT

##### P.1 Description of the Composition of the Drug Product

- **Description of drug product**

The drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution that is packaged in low density polyethylene (LDPE) bottles, with (b) (4) (b) (4) tips and (b) (4) caps. Each unit is filled with 5 mL of the sterile solution at a concentration of 0.24%.

- **Drug product composition**

The proposed drug product composition is provided in Table 3.2.P.1-1 of the subject submission, which has been reproduced below:

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Latanoprostene bunod <sup>a</sup>	In-house	Active	0.24
Benzalkonium chloride (BAK), (b) (4)	NF	(b) (4) Preservative	(b) (4) <sub>b</sub>
Polysorbate 80 (b) (4)	NF	(b) (4)	(b) (4)
Edetate disodium (b) (4)	USP		
Sodium citrate (b) (4)	USP		
Citric acid (b) (4)	USP		
Glycerin	USP		
Water (b) (4)	USP		
	(b) (4)		
	(b) (4)		

a This ingredient is (b) (4)

b This amount is equivalent to 0.20 mg/mL BAK in the final formulation.

NF = National Formulary  
USP = United States Pharmacopeia

(b) (4)

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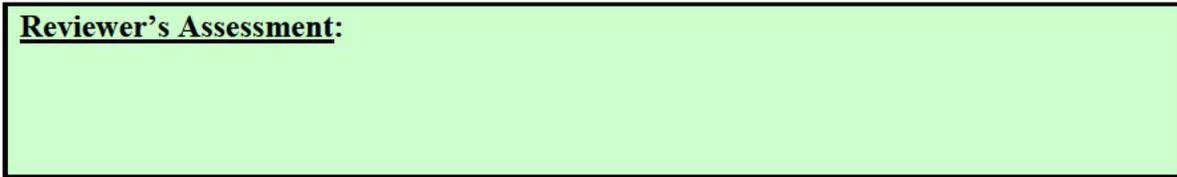
- A APPENDICES**
- A.2 Adventitious Agents Safety Evaluation**
    - A.2.1 Materials of Biological Origin**
    - A.2.2 Testing at Appropriate Stages of Production**
    - A.2.3 Viral Testing of Unprocessed Bulk**
    - A.2.4 Viral Clearance Studies**
- R REGIONAL INFORMATION**
- R.1 Executed Batch Record**
- 2. REVIEW OF COMMON TECHNICAL DOCUMENT-  
QUALITY (CTD-Q)  
MODULE 1**
- A. PACKAGE INSERT**
- ADEQUATE**
- REVIEWER COMMENT –**
- 3. LIST OF MICROBIOLOGY DEFICIENCIES AND  
COMMENTS:**

**2.3.P.7 Container/Closure System**

4. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Applicant's Response:**

**Reviewer's Assessment:**

**A APPENDICES****A.2 Adventitious Agents Safety Evaluation**

5. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

**Applicant's Response:**

**Reviewer's Assessment:**



6. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:**

**Reviewer's Assessment:**

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:**

**Secondary Review Comments and Concurrence:**

## ASSESSMENT OF ENVIRONMENTAL ANALYSIS

7. Is the applicant's claim for categorical exclusion acceptable?
  
8. Is the applicant's Environmental Assessment adequate for approval of the application?

### **Applicant's Response:**

The applicant requested a categorical exclusion from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.31(b) on the grounds that the concentration at the point of entry into the aquatic environment is expected to be less than 1 ppb. The applicant had not provided an explicit statement that, to their knowledge, no extraordinary circumstances exist. The applicant was notified and an adequate statement was provided.

**Reviewer's Assessment: Adequate.** The categorical exclusion is appropriate for the anticipated amount of drug to be used, and a statement regarding the applicant's knowledge of extraordinary circumstances has been provided. The claim for a categorical exclusion from an EA is acceptable by Environmental Officer Dr. James Laurenson in the email communication dated on 9/30/2015.

## OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

### **Reviewer's Assessment and Signature:**

**Adequate.**

**Chunchun Zhang, Ph.D.; Reviewer Chemist; Branch 3; Division of New Drug Product I.**

**Mar 11, 2016.**

### **Secondary Review Comments and Concurrence:**

**I concur Mar 11, 2016.**

**Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.**

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1  
Labeling & Package Insert**

**1. Package Insert**

**(a) “Highlights” Section (21CFR 201.57(a))**

**VESNEO™** (latanoprostene bunod ophthalmic solution) 0.024%

----- DOSAGE FORMS AND STRENGTHS -----

- <sup>(b) (4)</sup> topical ophthalmic solution <sup>(b) (4)</sup> latanoprostene bunod 0.24 mg/mL.

Item	Information Provided in NDA	Reviewer’s Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths		Adequate

**Conclusion: Adequate.**

**(b) “Full Prescribing Information” Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

**VESNEO** is a <sup>(b) (4)</sup> topical ophthalmic solution containing latanoprostene bunod 0.24 mg/mL.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

**Conclusion: Adequate.**

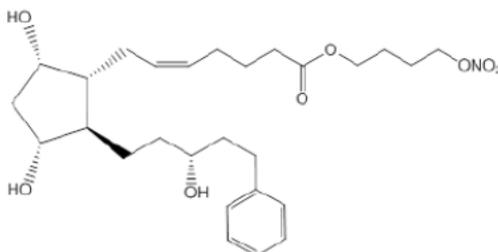
**#11: Description (21CFR 201.57(c)(12))**

VESNEO™ (latanoprostene bunod ophthalmic solution) 0.024% is a (b) (4) (b) (4) prostaglandin (b) (4) formulated as a sterile topical ophthalmic solution (b) (4). VESNEO contains the active ingredient latanoprostene bunod 0.24 mg/mL, the preservative benzalkonium chloride 0.2 mg/mL, and the following inactive ingredients: polysorbate 80, glycerin, EDTA, and water. The formulation is buffered to pH 5.5 with citric acid/sodium citrate.

Its chemical name is 4-(Nitrooxy)butyl (5Z)-7-{{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}}hept-5-enoate. Its molecular formula is C<sub>27</sub>H<sub>41</sub>NO<sub>8</sub>.

**Molecular weight: 507.62.**

Its chemical structure is:



Latanoprostene bunod is a colorless to yellow oil.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Adequate
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Adequate
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class		Adequate
Chemical name, structural formula, molecular weight		Molecular weight is missing in the original NDA submission.
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		N/A

**Conclusion: Adequate.** Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

Delivery System:

(b) (4)

**VESNEO™** (latanoprostene bunod ophthalmic solution) 0.024% is supplied in a natural LDPE bottle with dropper tip and a turquoise cap (b) (4):

- 7.5 mL with a 5 mL fill volume (NDC 24208-504-05)

Storage:

(b) (4) at 2° to 8 °C (36° to 46°F).

Protect from light.

Protect from freezing.

Once a bottle is opened (b) (4), it may be stored at (b) (4) to 25°C (77°F) for 8 weeks.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		Adequate
Storage conditions		Adequate

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Adequate

**Conclusion: Adequate.** Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

**2. Container and Carton Labeling**

**1) Immediate Container Label**

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration (21.CFR 201.100(b)(3))		Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		N/A
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		N/A

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

\*\*Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion: Adequate.** All the information required to appear on the immediate container label appears on the carton.

## 2) Carton Labeling

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[ 201.10(a),		Adequate
Sterility Information (if applicable)		Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		N/A

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Adequate
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**Conclusion: Adequate.** Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

### OVERALL ASSESSMENT AND SIGNATURES: LABELING

**Reviewer's Assessment and Signature:**

Adequate.

**Chunchun Zhang, Ph.D.; Reviewer Chemist; Branch 3; Division of New Drug Product I.**

**Mar 11, 2016.**

**Secondary Review Comments and Concurrence:**

**I concur Mar 11, 2016.**

**Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.**

# Product Quality Microbiology Review

30 Mar 2016

**NDA:** 207795/N-000

**Drug Product Name**

**Proprietary:** Vesneo™

**Non-proprietary:** latanoprostene bunod

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Submit	Received	Review Request	Assigned to Reviewer
21 Jul 2015	21 Jul 2015	N/A	07 AUG 2015
23 Dec 2015	23 Dec 2015	N/A	N/A
11 Mar 2016	11 Mar 2016	N/A	N/A

**Applicant/Sponsor**

**Name:** Bausch & Lomb Inc.

**Address:** 400 Somerset Corporate Boulevard  
Bridgewater, NJ 08807  
USA

**Representative:** Isabelle B. Lefebvre, MSc.RA, RAC EU & US.  
Sr. Director, US Regulatory Affairs

**Telephone:** (908) 541-3065

**Name of Reviewer:** Daniel J. Schu, Ph.D.

**Conclusion:** This submission is recommended for approval on the basis of sterility assurance.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
  2. **SUBMISSION PROVIDES FOR:** Request to market a new drug
  3. **MANUFACTURING SITE:** Bausch & Lomb, Inc.  
8500 Holden River Parkway  
Tampa, FL 33637
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Sterile, preserved solution in 7.5 mL dropper bottle
    - Topical ocular
    - 0.024%
  5. **METHOD(S) OF STERILIZATION:** (b) (4)  
(b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** This drug product is indicated for “reduction of intraocular pressure for patients with open-angle glaucoma of ocular hypertension.”
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:** This submission was provided in the eCTD format.

A Microbiology information request was forwarded to the applicant by the OPQ Project Manager on 14 December 2015. The applicant amended the application with responses to this information request on 23 December 2015. Applicant responses are summarized and reviewed in Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.

A Microbiology information request was forwarded to the applicant by the OPQ Project Manager on 19 February 2016. The applicant amended the application with responses to this information request on 11 March 2016. Applicant responses are summarized and reviewed in appropriate sections of this review.

filename: 207795.doc

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability - NDA 207795 is recommended for approval on the basis of product quality microbiology.**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A.**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4)

(b) (4)

- B. Brief Description of Microbiology Deficiencies - There are no microbiology deficiencies identified.**
- C. Contains Potential Precedent Decision(s)-  Yes  No**

**III. Product Quality Microbiology Risk Assessment**

**A. Initial Product Quality Microbiology Risk Assessment**

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O <sup>(3,4,5)</sup>	Severity of Effect (S)	Detect. (D)	Risk Priority Number <sup>6</sup> (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)						

\*Anti-Microbial Formulation (meets USP<51>)

1 = (b) (4)

2 = (b) (4)

(b) (4)

(b) (4)

3 = [redacted] (b) (4)  
(b) (4)  
4 = [redacted] (b) (4)  
5 = [redacted] (b) (4)  
6 = [redacted] (b) (4)

**B. Final Risk Assessment** - The proposed manufacturing process poses minimal risk to the microbiological quality of the subject drug product.

**IV. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_  
Daniel J. Schu, Ph.D.

**B. Endorsement Block** \_\_\_\_\_  
Jessica G. Cole, Ph.D.  
Microbiology Quality Assessment Lead (Acting)

**C. CC Block**  
Panorama

Daniel J. Schu -S  
(Affiliate)

Digitally signed by Daniel J. Schu -S (Affiliate)  
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH,  
ou=People, 0.9.2342.19200300.100.1.1=0014362959,  
cn=Daniel J. Schu -S (Affiliate)  
Date: 2016.03.30 11:17:10 -04'00'

Jessica Cole -S

Digitally signed by Jessica Cole -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, cn=Jessica Cole -S,  
0.9.2342.19200300.100.1.1=2000397920  
Date: 2016.03.30 12:38:20 -04'00'

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Gaetan Ladouceur, Methods Validation Requestor, CMC Reviewer  
Chunchun Zhang, Methods Validation Requestor, CMC Reviewer  
Anamitro Banerjee, CMC Lead  
Navi Bhandari, Methods Validation Project Manager  
Office of New Drug Product  
E-mail Address: [gaetan.ladouceur@fda.hhs.gov](mailto:gaetan.ladouceur@fda.hhs.gov) [Chunchun.zhang@fda.hhs.gov](mailto:Chunchun.zhang@fda.hhs.gov)  
Phone: 301-796-3878 301-796-5168

**FROM:** FDA  
Division of Pharmaceutical Analysis  
Laura C. Pogue, MVP Coordinator  
645 S Newstead Avenue  
St. Louis, MO 63110  
Phone: (314) 539-2155

**Through:** David Keire, Ph.D., CDER/OPQ/OTR/DPA , Lab Chief, Branch I  
Phone: (314) 539-3850

**SUBJECT:** Methods Validation Report Summary

---

Application Number: NDA 207795

Name of Product: Latanoprostene Bunod Ophthalmic Solution, 0.024%

Applicant: Bausch and Lomb, Inc

Applicant's Contact Person: Isabelle Lefebvre

Address: 400 Somerset Corporate Boulevard, Bridgewater, NJ 08807

Telephone: 908-541-3065 Email: [isabelle.lefebvre@bausch.com](mailto:isabelle.lefebvre@bausch.com)

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Date Methods Validation Consult Request Form Received by DPA: 09/01/2015

Date Methods Validation Package Received by DPA: 09/01/2015

Date Samples Received by DPA: 10/02/2015

Date Analytical Completed by DPA: 11/25/2015

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



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Date: November 25, 2015

To: Gaetan Ladouceur, CMC Reviewer  
Chunchun Zhang, CMC Reviewer  
Anamitro Banerjee, CMC Lead  
Navi Bhandari, Methods Validation Project Manager

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA  
Anjanette P. Smith, Chemist, CDER/OPQ/OTR/DPA

Through: David Keire Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

Subject: Method Verification of NDA 207795: Latanoprostene Bunod Ophthalmic Solution, 0.024%

**The following methods were verified and found acceptable for quality control and regulatory purposes:**

- 1) 3.2. S.4.2 Analytical Procedure for Assay and Related Substance by UPLC from Bausch & Lomb Incorporated Chemical Specification page 1-18, Chem. Spec. C-1928 Rev. 01, Effective date: 04/06/2015.
- 2) 3.2. S.4.2 Analytical Procedure for [REDACTED] <sup>(b) (4)</sup> in Latanoprostene Bunod by HPLC from Bausch & Lomb Incorporated Chemical Specification page 1-10, Chem. Spec. C-1929 Rev. 01, Effective date: 11/08/2015.
- 3) 3.2. P.5.2 and 3.2. P.5.3 Analytical Procedure- Identification, Assay, and Related Substances by UPLC from Bausch & Lomb Incorporated Chemical Specification page 1-10, Chem. Spec. C-1876 Rev. 01, Effective date: 28/09/2015.

Analyst Worksheets are available in ECMS: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c25e03>

**Summary of Analysis:**

**1) 3.2. S.4.2 Analytical Procedure for Assay and Related Substance by UPLC-C1928: Identification, Assay and Relative Substance of Latanoprostene Bunod Active Pharmaceutical Ingredient.**

% Assay from 3 sample preparations:

	Sample -1	Sample -2	Sample -3
% Assay as is	(b) (4)		
% Assay corrected	(b) (4)		
<b>Average of % Assay</b>	(b) (4)		
Specifications	(b) (4) %/Pass		

Calculation for Related Substance in Latanoprostene Bunod API

(b) (4)

Identification of Latanoprostene Bunod in API by UPLC

(b) (4)

**2) 3.2. S.4.2 Analytical Procedure for (b) (4) in Latanoprostene Bonud by HPLC- C1929: Determination of area % of (b) (4) in Latanoprostene Bunod Active Pharmaceutical Ingredient.**

RRT	Average (2) of % Isomeric Imp.	Specifications
(b) (4)		

**3) 3.2. P.5.2 and 3.2. P.5.3 Analytical Procedure- Identification, Assay, and Related Substances by UPLC: Identification, assay, and determination of related substances of LATANOPROSTENE BUNOD OPHTHALMIC SOLUTION 0.024%**

Assay	%LC	Specifications
Latanoprostene bunod	(b) (4)	(b) (4) %, Pass
<b>Related Substances</b>	<b>RRT</b>	<b>%RS</b>
<b>(Release, Shelf-Life) Specifications</b>		
(b) (4)		

Identification of Latanoprostene Bunod in the drug product by UPLC

(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.**  
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/s/  
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LAURA POGUE  
11/25/2015

DAVID A KEIRE  
11/25/2015

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Application #: 207795      Submission Type: 505(b)(1)

Established/Proper Name:  
**VESNEO™ (latanoprostene  
 bunod ophthalmic solution)**  
 0.024%

Applicant: Bausch &  
 Lomb Inc.

Letter Date: July 21, 2015

Dosage Form: Solution

Chemical Type: NME

Stamp Date: July 21, 2015

Strength: 0.024%

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?			<p><i>We note in Section P.2 that (b) (4) configurations (b) (4) (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.</i></p> <p><i>For the environmental assessment section, no statement regarding extraordinary circumstances was provided, per 21 CFR 25.15(a) and (d).</i></p>

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

<b>B. NOTEWORTHY ELEMENTS OF THE APPLICATION</b>		<b>Yes</b>	<b>No</b>	<b>Comment</b>
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	Lyophilized product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>
37.		Microbial	<input checked="" type="checkbox"/>	<input type="checkbox"/>
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A. The formulation is an ophthalmic solution.
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Appropriate categorical exclusion request provide. However, no statement of extraordinary circumstances provided per 21 CFR 25.15(a) and (d).
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS				
	review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>			
FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <li><input type="checkbox"/> Name of facility,</li> <li><input type="checkbox"/> Full address of facility including street, city, state, country</li> <li><input type="checkbox"/> FEI number for facility (if previously registered with FDA)</li> <li><input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person.</li> <li><input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and</li> <li><input type="checkbox"/> DMF number (if applicable)</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <li><input type="checkbox"/> Is a manufacturing schedule provided?</li> <li><input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

<b>C. FILING CONSIDERATIONS</b>				
	<ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture                             <ul style="list-style-type: none"> <li>○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li>○ Includes complete description of product lots and their uses during development – BLA only</li> </ul> </li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance                             <ul style="list-style-type: none"> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> </li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability                             <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> </ul>			
<b>DRUG PRODUCT INFORMATION</b>				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots</li> <li>○ Includes complete description of product lots and their uses during development</li> </ul> </li> <li><input type="checkbox"/> Manufacture                             <ul style="list-style-type: none"> <li>○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> </li> <li><input type="checkbox"/> Control of Excipients</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	<input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> <li>○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Analytical validation package for release test procedures, including dissolution</li> </ul> <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> <input type="checkbox"/> Stability <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> <li>• Does the application contain the complete BA/BE data?</li> <li>• Are the PK files in the correct format?</li> <li>• Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This NDA does not contain, nor require a BA or BE study. Study # 809 is a PK study, which will be reviewed by OCP.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The formulation used in the Phase 3 clinical trial and the proposed commercial formulation are the same (Table 3.2.P.2.2-9)
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	This NDA does not contain, nor require a biowaiver request
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA, It is an ophthalmic solution formulation (immediate release).

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA, It is an ophthalmic solution formulation (immediate release).
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	There is no claim for BCS I designation in this application.
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <li><input type="checkbox"/> facilities and equipment                             <ul style="list-style-type: none"> <li>o manufacturing flow; adjacent areas</li> <li>o other products in facility</li> <li>o equipment dedication, preparation, sterilization and storage</li> <li>o procedures and design features to prevent contamination and cross-contamination</li> </ul> </li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:                             <ul style="list-style-type: none"> <li>o avoidance and control procedures</li> <li>o cell line qualification</li> <li>o other materials of biological origin</li> <li>o viral testing of unprocessed bulk</li> <li>o viral clearance studies</li> <li>o testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <li><input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:                             <ul style="list-style-type: none"> <li>o LAL instead of rabbit pyrogen</li> <li>o Mycoplasma</li> </ul> </li> <li>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</li> </ul>				

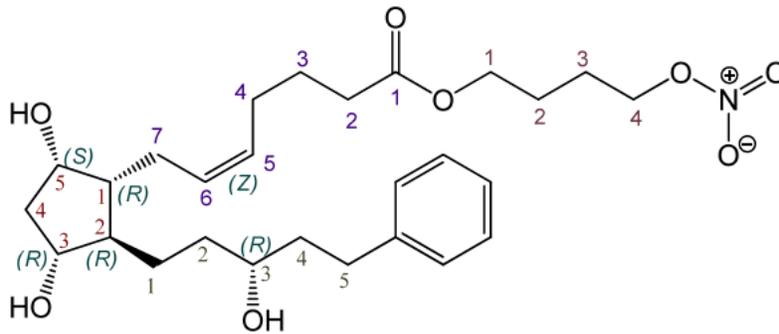
Latanoprostene Bunod Ophthalmic Solution, 0.024% drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye. This product is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma and ocular hypertension.

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

The drug substance is an NME. The drug substance is metabolized locally to form two active species: latanoprost acid and nitric oxide. The applicant has requested priority review.

The applicant is requesting categorical exclusion from EA under 21 CFR 25.31(b).



### *Latanoprostene bunod*

(Z)-4-(nitrooxy)butyl 7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R)-3-hydroxy-5-phenylpentyl)cyclopentyl)hept-5-enoate

Chemical Formula:  $C_{27}H_{41}NO_8$

Molecular Weight: 507.62

### **Drug Substance**

The drug substance is colorless pale yellow viscous oil that is soluble in organic liquids but insoluble in water. It has 5 chiral centers. The drug substance is manufactured by (b) (4),

(b) (4). The drug substance is (b) (4)

(b) (4) The applicant provided specifications for starting materials, solvents, and reagents. The applicant provided a description of the manufacturing process, in-process controls, process validation for three batches. The applicant provided MS, NMR (b) (4), and ATR-FTIR data in support of the proposed structure. The drug substance specification is (b) (4). The applicant provided a list of potential impurities in the drug substance (process as well as degradants) and identified two possible genotoxic impurities (b) (4). The acceptance limits for impurities are (b) (4). P/T reviewer should be consulted in this. (b) (4)

(b) (4) Batch data for 3 DS batches provided. Container closure: (b) (4). Stability data for 6 batches (b) (4) lots stored under long term (b) (4) and accelerated (b) (4) were provided (long term data for (b) (4) for (b) (4) batches and (b) (4) for (b) (4) batches).

### **Specifications for Latanoprostene Bunod at Release and Retest**

**OFFICE OF PHARMACEUTICAL QUALITY**  
**FILING REVIEW**

Test	Procedure	Acceptance Criteria
Appearance <sup>a</sup>	Visual	Colorless to pale yellow viscous oil
Identification A	Current USP, IR absorption	(b) (4)
Identification B	UPLC, C-1928	(b) (4)
Water Content by Karl Fischer	Current USP	NMT (b) (4)%
Residue on Ignition	Current USP	NMT (b) (4)%
Heavy Metals	Current USP	NMT (b) (4)
Assay "as is" <sup>a</sup>	UPLC, C-1928	(b) (4) %
Related Substances <sup>a</sup>	UPLC, C-1928	(b) (4) NMT (b) (4) % NMT % NMT % Any other single unspecified impurity: NMT % Total unspecified impurities: NMT %
Isomeric Impurities <sup>a</sup>	HPLC, C-1929	(b) (4) NMT (b) (4) % NMT %
Total Impurities <sup>a</sup>	UPLC, C-1928 and HPLC C-1929	Sum of individual related substances and isomeric impurities: NMT %
Residual Solvents	GC, C-1952	(b) (4)

a These tests are also performed at retest to ensure suitability for use in manufacture of drug product.  
NMT = not more than

**Drug Product**

The drug product is manufactured, tested, and packaged at the B/L facility in Tampa, FL. Four additional testing and one additional testing and sterilization sites are listed. All are located (b) (4). No novel excipients or excipients with human or animal origin are used. All the excipients are compendial grade

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

and within the IID limits. Apart from the API, BAK (b) (4), glycerin (b) (4), polysorbate 80 (b) (4), EDTA, (b) (4) citrate buffers (b) (4) constitutes the drug product. The product is packed in LDPE 7.5 mL bottles with (b) (4) tips and (b) (4) caps (fill: 5 mL).

### Qualitative and Quantitative Formulation of Latanoprostene Bunod Ophthalmic Solution, 0.024%

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Latanoprostene bunod <sup>a</sup>	In-house	Active	0.24
Benzalkonium chloride (BAK), (b) (4)	NF	(b) (4) Preservative	(b) (4)
Polysorbate 80 (b) (4)	NF	(b) (4)	(b) (4)
Edetate disodium (b) (4)	USP	(b) (4)	(b) (4)
Sodium citrate (b) (4)	USP	Buffering agent	(b) (4)
Citric acid, (b) (4)	USP	Buffering agent	(b) (4)
Glycerin	USP	(b) (4)	(b) (4)
Water (b) (4)	USP	(b) (4)	(b) (4)

a This ingredient is (b) (4)

b This amount is equivalent to 0.20 mg/mL BAK in the final formulation.

NF = National Formulary

USP = United States Pharmacopeia

The applicant provided a description of the manufacturing process. The proposed commercial scale are (b) (4). The manufacturing process involves (b) (4)

(b) (4) Analytical method description and validation data for non-compendial methods are provided. Batch data for several clinical and registration batches show no OOS result.

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## FILING REVIEW

### Release and Shelf-life Specification of Latanoprostene Bunod Ophthalmic Solution, 0.024%

Test	Procedure	Release Criteria	Shelf Life Criteria
Appearance	Visual	Clear and colorless to slightly yellow solution	
Identification-A <sup>a</sup>	UPLC, C-1876	(b) (4)	Not tested
Identification-B <sup>a</sup>	UV, C-1876		Not tested
Assay (latanoprostene bunod)	(b) (4) UPLC (b) (4) (b) (4)	(b) (4) % of label claim (LC = 0.24 mg/mL)	
Related substances	UPLC, C-1876	(b) (4)	
		Individual Related Substances: NMT (b) (4) %	Individual Related Substances: NMT (b) (4) %
		Total Related Substances: NMT (b) (4) % <sup>e</sup>	Total Related Substances: (b) (4) % <sup>e</sup>
Benzalkonium chloride	UPLC, C-1875	(b) (4) % of label claim (LC = 0.20 mg/mL)	(b) (4) % of label claim (LC = 0.20 mg/mL)
pH	Current USP	(b) (4)	
Osmolality	Current USP	(b) (4) mOsm/kg	(b) (4) mOsm/kg
Particulate matter	Current USP	NMT (b) (4)	
Antimicrobial effectiveness <sup>c, d</sup>	Current USP	Not tested	Meets USP requirements
Sterility	Current USP	Meets USP requirements	
Weight loss/gain <sup>c</sup>	Manual	Not applicable	NMT (b) (4) %
Fill volume <sup>a, f</sup>	Weight check	NLT label claim	Not tested

a This test is required at time of release only

b

c

d

e

f

LC = label claim

NMT = Not more than

USP = United States Pharmacopeia

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Stability data for several batches (b) (4) provided under 12 M long term (5C/ambient) and 6M accelerated (25C/60%) conditions. (b) (4) impurities and weight loss are apparent for all the batches; however the values remained well within specifications. Two OOS on (b) (4) were reported: (b) (4) lot 186771 stored at 5°C for 3 months and lot 186761 stored at 25°C for 6 months in section P.8. The corrective and preventative actions taken to minimize these (b) (4) are described in 3.2.R.

### **Biopharmaceutics**

Vesneo™ (latanoprostene bunod ophthalmic solution) 0.024%, is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye. The Applicant submitted this NDA under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50. The formulation used in the Phase 3 clinical trials and the proposed commercial formulation are the same (Table 3.2.P.2.2–9). The Applicant submitted a Pharmacokinetics (PK) study (# 809), with an objective to evaluate the systemic pharmacokinetics (PK) and ocular and systemic safety and tolerability of latanoprostene bunod ophthalmic solution (0.024%) in healthy subjects with a normal ophthalmic history. This PK study will be reviewed by the OCP. No Biowaiver request has been submitted.

This NDA is fileable from the Biopharmaceutics perspective.

This NDA submission does not require further assessment from the OPQ-ONDP-Biopharmaceutics team. Therefore, this filing review concludes the Biopharmaceutics involvement for this NDA.

### **Initial Risk Assessment:**

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Sterility	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	<ul style="list-style-type: none"> <li>Non-sterile unit(s)</li> </ul>	4	5	5	100		H
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	<ul style="list-style-type: none"> <li>Excessive endotoxin level</li> </ul>	1	1	1	1	No endotoxin limit established for topical ophthalmic	L
Assay (API), stability	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	(b) (4)	3 (Mod stable drug)	2	1	6	Moderately Stable Drug: Low API concentration Total impurities < (b) (4)	L
Assay (preservative)	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	<ul style="list-style-type: none"> <li>Lack of effectiveness through shelf-life</li> </ul>	1 (Release) 1 (Stability)	1	1	1	Preservative used: 0.20 mg/mL benzalkonium chloride (Assay monitored in Specs at release and stability). Multidose.	L

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Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Assay (anti-oxidant)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Decrease in potency</li> </ul>					Not used	L
Uniformity of Dose (Fill Volume/Deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Insufficient dose</li> </ul>	4	3	1	12	Fill volume tested at release.	L
Osmolality	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Irritation</li> <li>• Edema</li> </ul>	2	2	2	8	Osmolality testing is performed (DP specifications).	L
pH-	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Irritation</li> </ul> <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div>	4	4	1	16	Testing is performed (DP specifications). pH is (b) (4) in DS specifications (b) (4)	L
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	<ul style="list-style-type: none"> <li>• Irritation</li> <li>• Embolism</li> </ul>	3	5	2	30	Tested in DP specifications.	M
Leachable extractables	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	<ul style="list-style-type: none"> <li>• Generation of impurities</li> </ul>	4	4	3	48	Test data provided	M

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Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
	<ul style="list-style-type: none"> <li>• Site</li> </ul>							
Appearance (Color/turbidity)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>		3	3	1	9		L

**Anamitro Banerjee -S** Digitally signed by Anamitro Banerjee -S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S  
 Date: 2015.09.14 17:47:29 -04'00'