CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206185Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 206185
Review # 3
July 23, 2018

Drug Name/Dosage Form	***XELPROS (latanoprost ophthalmic emulsion)***
Strength	*0.005%*
Route of Administration	*Topical Ophthalmic*
Rx/OTC Dispensed	*Rx*
Applicant	*Sun Pharma Global FZE*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	*5/7/2018*
Amendment	*6/13/2018*
Amendment	*6/19/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Milton Sloan	Balajee Shanmugam
Microbiology	Laura R. Wasil	Erika Pfeiler
Biopharmaceutics	Banu Zolnik	Jing Li
Process	Steve Rhieu	Maotang Zhou
Facility	Christina Capacci-Daniel	Ying Zhang
Regulatory Business Process Manager	Kristine Leahy	NA

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 206185, XELPROS (Latanoprost Ophthalmic emulsion), 0.005% was submitted on Jan 31, 2014 and a resubmission on Apr 09, 2015 and Jul 28, 2016. The Office of Process and Facilities issued an overall withhold recommendation for facilities on this NDA. Therefore, this application was not recommended for approval from the Product Quality perspective. A Complete Response Letter dated Nov 24, 2014, Jul 30, 2015, and Dec 19, 2016 was issued.

NDA 206185 was resubmitted in response to the Dec 19, 2016 Complete Response on May 7, 2018. NDA 206185, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product, latanoprost ophthalmic emulsion, 0.005%. All information request and review issues have been addressed and there are no pending approvability issues.

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approval" recommendation was entered in Panorama by the the Office of Process and Facilities (OPF) on 6-26-2018.

NDA 206185 is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

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

II. Summary of Quality Assessments

Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance is latanoprost, a pale yellow to yellow viscous oil. It is manufactured by (b) (4) The drug substance is referenced to DMF (b) (4) which was found adequate by Dr. Sharon Kelly on 7/12/2018.

ii. Drug Product Quality Summary

XELPROS (latanoprost ophthalmic emulsion), 0.005% is a prostaglandin F_{2a} analog indicated for reduction of elevated intraocular pressure in patients with open-angle glaucoma, or ocular hypertension. The proposed product is a sterile emulsion and packaged in a 5-mL clear LDPE dropper bottle with 2.5 mL fill

volume. It is administrated by one drop in the affected eye(s) once daily in the evening.

Refer to quality review #1 on 10/24/2014, quality review #2 on 7/27/2015, addendum #1 to review #2 on 6/17/2016, and addendum #2 to review #2 on 12/16/2016 for the detailed discussion. This IQA covers the proposed update in Module 3.2.S and 3.2.P sections in the resubmission submitted on 5/7/2018. The IQA includes the input from the OPQ discipline review teams including drug substance, drug product, manufacturing process, quality micro and facility.

The risk assessment for elemental impurities was provided in the resubmission and was found acceptable. The drug product container closure revision has been reviewed and found acceptable in addendum #1 of review #2 on 6/17/2016. The revised XELPROS label is reviewed and will be communicated to the clinical PM.

The manufacturing process for Latanoprost Ophthalmic Emulsion consists of (b) (4). Changes made to the proposed manufacturing process (b) (4) have been reviewed and found acceptable. Additionally, the resubmission includes the proposed changes of modification of the container/closure system and (b) (4). It is found acceptable from quality micro perspective.

All the manufacturing sites are adequate based on the manufacturing capabilities and inspection history. Therefore, OPF has provided an overall recommendation of "Approval" on 6/26/2018 in Panorama (see the screenshots below).

Project Overall Manufacturing Facility Statuses

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	6/26/2018	Pending	NDA-206185-ORIG-1-RESUB-29
Withhold	12/16/2016	Complete Response	NDA-206185-ORIG-1-RESUB-22
Withhold	6/17/2015	Complete Response	NDA-206185-ORIG-1-RESUB-18
Withhold	11/13/2014	Complete Response	NDA-206185-ORIG-1

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Association (per 356h)	Alert
Withhold Approval	11/14/2014	NDA-206185-ORIG-1	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		None
Approve Facility	10/7/2014	NDA-206185-ORIG-1	(b) (4)				CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	5/12/2015	NDA-206185-ORIG-1-RESUB-18					CSN NON-STERILE API BY CHEMIC...		None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18					CTL CONTROL TESTING LABORATOR...	PENDING	None
Approve Facility	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3007512695	676162401	110003680	SUN PHARMA ADVANCED RESEARCH COMPANY LIM...	CTL CONTROL TESTING LABORATOR...	ACTIVE	None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	PENDING	None
Withhold Approval	6/17/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	None
No Evaluation Necessary	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		None
No Evaluation Necessary	5/12/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Withhold Approval	12/16/2016	NDA-206185-ORIG-1-RESUB-22	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD	SLQ STERILE LIQUID (EXCLUDE S...		None
Approve Facility	6/26/2018	NDA-206185-ORIG-1-RESUB-29	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES, LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	None

A. Special Product Quality Labeling Recommendations (NDA only)

NA

B. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	H	(b) (4)	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L		L	
Assay (API), stability	Formulation Container closure[1] Raw materials	L		L	
Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L		L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M		L	
pH	Formulation Container closure[1] Process parameters Scale/equipment	L		L	

Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	M	(b) (4)	L	
Extractables/leachables	Formulation Container closure	M		L	

1 Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.
2 Post-approval stability protocol provides for testing of all quality attributes.

This NDA is recommended for approval from the Product Quality Perspective.

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 206185

Charles Jewell

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Date: 7/12/2018 09:16:03AM
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Sharon Kelly

Digitally signed by Sharon Kelly
Date: 7/12/2018 08:03:36AM
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Addendum #2 to Review #2 NDA 206-185 Resubmission

Date: July 9, 2018

To: **NDA 206-185**

Through: Balajee Shanmugam, Ph.D., Branch Chief, Division of New Drug Product I

From: Milton J. Sloan, Ph. D., Sr. Chemistry Reviewer, Division of New Drug Product I

Subject: NDA 206-185, XELPROS™ (Latanoprost Ophthalmic emulsion), 0.005%
SEQUENCE NUMBER: 0028

NDA 206-185, XELPROS™ (Latanoprost Ophthalmic emulsion), 0.005% was submitted by Sun Pharma Advanced Research Company, Ltd. (SPARC) on January 31, 2014 and a resubmission on April 09, 2015, July 28, 2016, and May 7, 2018. The Office of Process and Facilities issued an overall withhold recommendation for facilities on this NDA (21CFR314.125(b)(13). Therefore, this application was not recommended for approval from Product Quality perspective. A Complete Response Letter dated November 24, 2014 and on July 30, 2015, December 19, 2016 was issued to SPARC.

SUN, on behalf of SUN FZE, is resubmitting the NDA for Latanoprost ophthalmic emulsion 0.005%. The responses to the identified issues from the 19 December 2016 complete response letter are found in 1.11.4. Additional updates have been made to Module 3.2.S and 3.2.P sections to reflect updated manufacturing machinery, testing methods, specifications, and post-approval stability protocol. A detail summary of the changes made to the Quality section is included in 1.11.4 (see review notes).

This DP review covers the proposed changes for the labels and labeling and the risk assessment for elemental impurities included in the resubmission. The revised XELPROS label comments are provided in the review notes. The drug product container closure revision has been reviewed and found acceptable in Review Addendum#1 of Review #2 (June 17, 2016).

The risk assessment was evaluated and found acceptable. The NDA is recommended for Approval form the Drug Product perspective.

Memorandum Prepared by

_____ _____

Milton J. Sloan, Ph. D. Sr. Chemist Reviewer Date
{*See electronic signature page*}

For Concurrence:

_____ _____

Balajee Shanmugam, Ph. D. Branch Chief Date
Division of New Drug Product I
{*See electronic signature page*}

RISK ASSESSMENT FOR ELEMENTAL IMPURITIES

The report summarizes the product risk assessment set forth in ICH Q3D: Elemental Impurities using the principles of risk management described in ICH Q9 by evaluating potential elemental impurities in the product contributing from drug substance, excipients, water, manufacturing process equipment and container closure for Latanoprost Ophthalmic Emulsion, 0.005% w/v, 2.5 mL for US market. The total elemental impurities present in the drug substance, excipients, manufacturing process and equipment, and container closure system were assessed.

Table XI: Total Elemental Impurity Assessment

(b) (4)

The result of summation of each elemental impurity in the drug product as mentioned in Table XI is less than the control threshold (b) (4) as per USP <232> / ICH Q3D guideline. So, no further control is required in the drug product specification with respect to elemental impurities . Hence, it is concluded that levels of elemental impurities in Latanoprost Ophthalmic Emulsion, 0.005% w/v, 2.5 mL are within the safety recommendations of USP general chapter <232>/lCH Q3D guideline.

Reviewer's Assessment: Adequate

The reports demonstrate the drug product does not exceed the PDEs for each identified elemental impurity per USP <232>/ICH Q3D.

LABELING

Highlights of Prescribing Information

XELPROS (latanoprost ophthalmic emulsion) 0.005%
For Topical Ophthalmic Use

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic emulsion containing 50 mcg/mL of latanoprost (0.005%). (3)

Reviewer's Assessment: Adequate

FULL PRESCRIBING INFORMATION: CONTENTS

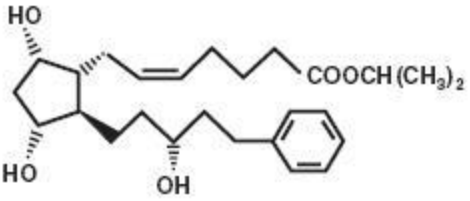
3 DOSAGE FORMS AND STRENGTHS
(b) (4) ophthalmic emulsion containing 50 mcg/mL latanoprost.

Reviewer's Assessment: Adequate

11 DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5- heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:

M.W. 432.58



Latanoprost is a pale yellow to yellow viscous oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

XELPROS (latanoprost ophthalmic emulsion) 0.005% is a sterile, isotonic, buffered aqueous emulsion of latanoprost with a pH approximately 7.0 and an osmolality of approximately 375mOsmol/kg. Each mL of XELPROS contains 50 micrograms of latanoprost. Potassium sorbate 0.47% is added as a preservative. The inactive ingredients are: castor oil, sodium borate, boric acid, propylene glycol, edetate disodium, polyoxyl 15 hydroxystearate, sodium hydroxide,

hydrochloric acid, and water for injection. One drop contains approximately 1.5 mcg of latanoprost.

Reviewer's Assessment: Adequate

16 HOW SUPPLIED/STORAGE AND HANDLING

XELPROS (latanoprost ophthalmic emulsion) is supplied as an off-white to pale yellow, translucent, isotonic, sterile, buffered emulsion of latanoprost 0.005% (50 mcg/mL). It is supplied as a 2.5 mL emulsion filled in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, and a turquoise high density polyethylene pilfer-proof cap. Each mL contains 50 mcg of latanoprost.

2.5 mL fill, 0.005% (50 mcg/mL)

Package of 1 bottle	NDC 47335-317-90
Multi-Pack of 3 bottles	NDC 47335-317-92

Storage: Protect from light. Store (b) (4)

(b) (4)

Reviewer's Assessment:
In use stability studies were done at room temperature up 45 days. Chemical and physical in use stability has been demonstrated for 45 days at 25 C for the opened container. From microbiological view point, the micro quality data was not reported with this study. However, from the Micro review that AET was done up to 45 days and is justified from the microbiological point of view.

Immediate Container Label

{copy/paste or refer to a representative example of a proposed container label}

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Milton Sloan

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Date: 7/10/2018 12:09:32PM
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Balajee Shanmugam

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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 206185 Resubmission 29

Drug Product Name / Strength: Latanoprost Ophthalmic (b) (4) 0.005% w/v

Route of Administration: Ophthalmic

Applicant Name: Sun Pharma Global FZE

Manufacturing Site: Sun Pharmaceutical Industries, Ltd., Halol-Baroda Highway, Halol, Gujarat 389350, India

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: The manufacturing process remains unchanged. The proposed changes include modification of the container/closure system (b) (4) (b) (4). The application is recommended for approval on the basis of product sterility assurance.

List Submissions Being Reviewed: 5/7/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is an eCTD submission. The previous submission was recommended for approval by the quality microbiology reviewer (N N206185N000R1.doc, dated 26 September 2014). However, the current resubmission indicates changes to existing quality information (i.e. modified CCS and (b) (4)) that require assessment. The requalification of the (b) (4) was previously reviewed and deemed adequate in a79001s014mr01.pdf, dated 05 December 2016.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug product is sterilized during the manufacturing process. The drug substance was not reviewed.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is an off-white/pale yellow, translucent, isotonic, sterile (b) (4) that is preserved with 0.47% w/v potassium sorbate.
- **Drug product composition** – There are no proposed changes to the drug product composition.
- **Description of container closure system** – The drug product is packaged as a 2.5mL (b) (4) in a multiple-use 5mL (b) (4) low-density polyethylene bottle (b) (4) having a (b) (4) LDPE dropper tip and a (b) (4) turquoise (b) (4) high density polyethylene (HDPE) (b) (4) screw cap.

CHANGES PROPOSED IN THIS RESUBMISSION

NDA 206185 was previously reviewed and deemed adequate from the perspective of product quality microbiology on 26 September 2014 (N206185N000R1.doc). However, the NDA received a complete response and has since been resubmitted three times, with the most recent submission on 07 May 2018. While the applicant's response to the CR letter did not include responses directed to quality microbiology, the applicant made changes to existing quality information that require assessment. The changes that will be subject to this review are as follows:

1. Modification of the container/closure system.
2. (b) (4)

INFORMATION TO SUPPORT THE PROPOSED CHANGES

(b) (4)

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List of Deficiencies: Not applicable.

Primary Microbiology Reviewer Name and Date: Laura R. Wasil, PhD; 17 July 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Erika Pfeiler; 20 June 2018

Erika Pfeiler

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Laura Wasil

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Chunchun Zhang

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Chunchun Zhang

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NDA 206185

Product Quality Assessment (Addendum #3 to Review #2)

From: Chunchun Zhang, ATL/Acting CMC Lead, Branch 3, ONDP/OPQ

Date: Dec-16-2016

Re: NDA 206185, XELPROS™ (latanoprost ophthalmic emulsion) 0.005%

Response to FDA Complete Response Letter submitted on July 28, 2016 (SD 22)

NDA 206-185, XELPROS™ (latanoprost ophthalmic emulsion) 0.005% was submitted by Sun Pharma Advanced Research Company, Ltd. (SPARC) on January 31, 2014 and a resubmission on April 09, 2015 following the first cycle CR action. The Office of Process and Facilities issued an overall "Withhold" recommendation for facilities on this NDA. Therefore, this application was not recommended for approval from Product Quality perspective. A Complete Response Letter dated November 24, 2014 and subsequently on July 30, 2015 was issued to SPARC.

In response to the July 30, 2015 CR, SPARC submitted a resubmission on July 28, 2016. However, the outcome of the most recent inspection of drug product manufacturing facility Sun Pharmaceutical Industries Ltd., FEI# 3002809586 (Halol site) has resulted in Office of Process and Facilities recommending "Withhold" as documented in the NDA-206185-ORIG-1-RESUB-22 project (see screenshots attached).

Therefore, NDA 206185 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. No new or updated Product Quality information was submitted in the resubmission and therefore a separate Product Quality review will not be written. This Addendum covers the Product Quality aspect of the resubmission.

The following CR statement on the unacceptable status of the manufacturing facility (Sun Pharmaceutical Industries Ltd.) should be included in the CR letter:

During a recent inspection of the Sun Pharmaceutical Industries Ltd., FEI# 3002809586, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Chunchun Zhang, Ph.D.
ATL for 206185

Manufacturing facility status:

Project Overall Manufacturing Facility Statuses

Overall Status	Completion Date	Submission Status	Project Name
Withhold	12/16/2016	Pending	NDA-206185-ORIG-1-RESUB-22
Withhold	6/17/2015	Complete Response	NDA-206185-ORIG-1-RESUB-18
Withhold	11/13/2014	Complete Response	NDA-206185-ORIG-1

Note current pOAI alert for Sun Pharmaceutical Industries Ltd. (FEI 3002809586):

Program Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Association (per 356h)	Alert
Withhold Approval	11/14/2014	NDA-206185-ORIG-1	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of
Approve Facility	10/7/2014	NDA-206185-ORIG-1	(b) (4)				CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	5/12/2015	NDA-206185-ORIG-1-RESUB-18					CSN NON-STERILE API BY CHEMIC...		None
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18					CTL CONTROL TESTING LABORATOR...	PENDING	None
Approve Facility	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3007512695	676162401	110003680	SUN PHARMA ADVANCED RESEARCH COMPANY LIM...	CTL CONTROL TESTING LABORATOR...	ACTIVE	None
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	PENDING	None
Withhold Approval	6/17/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD.	SLQ STERILE LIQUID (EXCLUDE S...	ACTIVE	Potential Official Action Indicated as of
No Further Evaluation	4/28/2015	NDA-206185-ORIG-1-RESUB-18	3002809586	719638124	110002606	SUN PHARMACEUTICAL INDUSTRIES LIMITED	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of
No Further Evaluation	5/12/2015	NDA-206185-ORIG-1-RESUB-18	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Withhold Approval	12/16/2016	NDA-206185-ORIG-1-RESUB-22	3002809586	725959238	110002606	SUN PHARMACEUTICAL INDUSTRIES LTD	SLQ STERILE LIQUID (EXCLUDE S...		Potential Official Action Indicated as of

Chunchun Zhang

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MEMORANDUM

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

DATE: 07 December 2016

TO: Chunchun Zhang
CDER/OPQ/ONDP/DNDPI/NDPBIII

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/Branch 1

THROUGH: John Arigo, Ph.D.
Acting Branch Chief
CDER/OPQ/OPF/DMA/Branch 1

SUBJECT: NDA 206185 Resubmission, 28 July 2016

The subject NDA describes latanoprost ophthalmic (b) (4), a sterile (b) (4) for topical ophthalmic administration. It contains 0.47% potassium sorbate as an antimicrobial preservative.

NDA 206185 was originally submitted on 31 January 2014. A microbiology review was completed and archived in DARRTS on 26 September 2014, recommending approval. The review described successful completion of antimicrobial effectiveness testing, per USP <51> with preservative content as low as (b) (4)% of the label claim. AET was performed successfully as part of stability testing through 24 months. Additional in-use stability studies were described, which included an assay of the preservative content of the drug product over a 45-day simulated in-use period. The preservative content of the product was within (b) (4)% at all timepoints. A (b) (4) in-use period was described in the product's label in the initial submission.

The NDA ultimately received a complete response, and has been resubmitted twice, most recently on 28 July 2016. While this resubmission did not contain new quality microbiology information, a request was made for DMA review regarding the proposed in-use period in the draft prescribing information. The in-use period is the same as was initially proposed (b) (4).

Reviewer's Comment: There is currently no consensus on the type of study expected to extend the in-use period of multi-dose products for more than the 28 day period defined in the USP <51> test method. This applicant has performed studies to demonstrate that the preservative content level remains stable over a 45-day in-use period, and this study is considered sufficient to support the microbiological quality of the product over a (b) (4) period.

Acceptable

Chemistry Assessment Section

Addendum #1 to Review #2 NDA 206-185

Date: June 17, 2016

To: **NDA 206-185**

Through: Balajee Shanmugam, Ph.D., Branch Chief (Acting), Division of New Drug Product I

From: Milton J. Sloan, Ph. D., Chemistry Reviewer, Division of New Drug Product I

Subject: NDA 206-185, XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005%
SEQUENCE NUMBER: 0020 Container Closure System

NDA 206-185, XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005% was submitted by Sun Pharma Advanced Research Company, Ltd. (SPARC) on January 31,2014 and a resubmission on April 09, 2015. The Office of Process and Facilities issued an overall withhold recommendation for facilities on this NDA (21CFR314.125(b)(13). Therefore, this application was not recommended for approval from Product Quality perspective. A Complete Response Letter dated November 24, 2014 and on July 30, 2015 was issued to SPARC.

On December 11 , 2015, FDA had a teleconference with Aron Shapiro, VP, Ora, Inc, SPARC's authorized US Representative, Jeffrey Coderre, Director, Regulatory Writing, Ora to inform of reports of problems with other ophthalmic products using the same cap closure system (same DMF (b) (4) as that used for XELPROS. The reports indicated that the breakaway plastic ring attached to the cap can fall off when the bottle is inverted over the eye. Ora on behalf of SPARC submitted a response to NDA 206185 (SN0019) on Feb 05, 2016 regarding the XELPROS cap closure system (CCS). In response to SN0019, the Agency had a teleconference with Ora on March 11 , 2016 and requested changes to the container closure system.

SPARC requested the ophthalmic bottle manufacturer for XELPROS to modify the bottle to keep the breakaway ring from falling off as per the Agency's recommendation while not changing any aspect of the bottle that contacts the drug product. As a result, the cap and bottle design have been modified to prevent the breakaway ring from falling off. (b) (4)

Chemistry Assessment Section

SPARC
1) SPARC seeks concurrence from the Division that the proposed modifications of the CCS adequately address all the requirements to prevent the ring from falling off upon bottle inversion.

FDA
We concur. The possibility of the (b) (4) cap's breakaway ring falling off the bottle has been addressed. The submitted information detailing modifications to the proposed container closure system (CCS) indicate the breakaway ring will be retained on the bottle.

SPARC
2) SPARC requests confirmation that as there was no change in the dimensions and MOC of the revised CCS, no additional stability testing is required with the proposed CCS.

FDA
Agree. The information provided confirms there are no changes to the physical dimensions and materials of construction (MOC) for the bottle, plug and cap of the revised CCS. No additional stability data is required to support a resubmission since the modifications does not contact the drug product. The design changes are minor and may be considered to have very minimal potential for adverse effect on the identity, strength, quality of potency of the product. The proposed stability protocol and stability commitment is in accordance with ICH Q1A(R) stability guideline and is acceptable.

Memorandum Prepared by

Milton J. Sloan, Ph. D. Chemist Reviewer Date
{*See electronic signature page*}

For Concurrence:

Balajee Shanmugam, Ph. D. Branch Chief(Acting) Date
Division of New Drug Product I
{*See electronic signature page*}

REVIEW NOTES

The comparative dimension and drawing (below) show how the design has been modified to prevent the ring from falling off while also showing that the material of construction (MOC), wall thickness, dimension and internal volume of the overall container closure system have not changed. Since these changes only impact the external part of the cap and bottle and will not be in contact with drug product, SPARC maintains that the already completed stability tests in the final product packaging are sufficient. Table 1 compares the original bottle design specifications to the new bottle design in a tabular format.

(b) (4)

(b) (4)

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

Chemistry Assessment Section

Table 1

Container Closure Comparison				
S. Nos.	**Parameters**	**Existing**	**Proposed**	**Remarks**
1	**Material of construction**	(b) (4)		No change
2	**PHYSICAL DIMENSIONS**			
I.	Bottle	(b) (4)		Change No change
II.	Plug			No change No change
III.	Cap			Change No change
IV.	Brimful Capacity			No change
V.	Nominal Capacity	5.0 mL	5.0 mL	No change
2.	Drop Size weight	30 mcl	30 mcl	No change
3.	Closing Torque	(b) (4)		No change
4.	Opening Torque (Avg)			No change
5.	Pull force Avg (N)			Change
6.	Engineering Drawing	Refer to Attachment II - (b) (4) (Existing Container closure system)	(b) (4) (Proposed Container closure system)	

Conclusion:

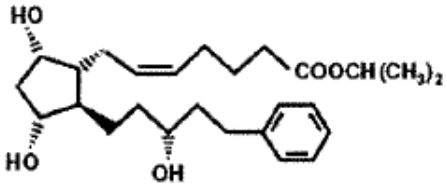
1. Material of construction is the same as existing Container closure system, hence no impact on stability.
2. Drawing no. have been changed for better clarity between existing and proposed Container closure system.
3. (b) (4)

Table 1 above compares the existing CCS and the proposed CCS parameters. The table show no changes to the material of construction and physical dimensions. The drawings are changed to reflect the minor modifications. (b) (4) (b) (4) (b) (4) The overall change is minimal and will not impact product quality.

NDA 206-185

XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005% w/v

Sun Pharma Advanced Research Company



Drug Product Reviewer: Milton J. Sloan, Ph.D.

ONDQA Pre-Marketing Assessment Division II Branch V

For Division of Transplant and Ophthalmology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-185

2. REVIEW #: 2

3. REVIEW DATE: 20-Jul-2015

4. REVIEWER: Milton J. Sloan, Ph.D.

Primary Review Team:

Reviewer	NDA Section
Mariappan Chelliah, Ph.D	Drug Substance: Lantanoprost, DMF
Milton Sloan, Ph.D.	Drug Product
Banu Zolnik, Ph.D.	Biopharmaceutics Review

Secondary:

Reviewer	Section
Balajee Shanmugam, Ph.D.	NDA

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	31-Jan-2014
Amendment	09-July-2014
Amendment	30-Sept-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	09-Apr-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Sun Pharma Advanced Research Company Limited
Address:	Tandalja, Vadodara, Gujarat, India 390020
Representative:	Aron Shapiro, Vice President, Ora, Inc. 300 Brickstone Square Andover, MA 01810

Telephone: (978) 685-8900

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: XELPROS
   b) Non-Proprietary Name (USAN): Latanoprost
   c) Code Name/# (ONDQA only): N/A
   d) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: 3,
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Prostaglandin analog

11. DOSAGE FORM: Ophthalmic emulsion

12. STRENGTH/POTENCY: 0.005% w/v (125µg/2.5mL)

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: _X__R_x ___OTC

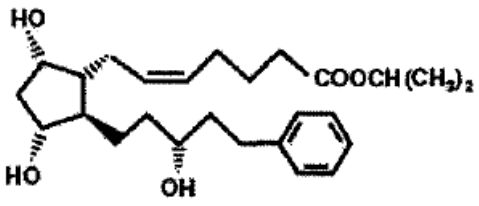
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name for Lantanoprost is: (5Z)-7-[(1R,2R,3R,5S)- 3,5-dihydroxy-2-[(3R)-3-hydroxy- 5-phenylpentyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester

Structural formula:



Molecular Formula: $C_{26}H_{40}O_5$
Molecular Weight: 432.61

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lantanoprost	1	Adequate	Reviewed by Dr, M. Chelliah (10/15/2014)	Please see Review #1
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	
(b) (4)	IV	(b) (4)		1	Adequate	Reviewed by Dr. J. Vidra (3/13/2014)	Please see Review #1

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-597	RLD
IND	102842	

18. STATUS:

OPQ:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
Facility Report (EES)	Withhold	June 17, 2015	
Pharm/Tox	Approval; Please see Review #1	Oct. 17, 2014	Maria Rivera, PhD.
Biopharm	Acceptable; Please see Review #1	Oct. 17, 2014	Banu Zolnik, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Not requested; Please see Review #1	N/A	N/A
DMEPA	Acceptable; Please see Review #1	Sept. 12, 2014	Rachna Kapoor, Pharm.D.
EA	Please see Review #1	Oct. 24, 2014	Milton Sloan, Ph.D.
Quality Microbiology	Approval; Please see Review #1	Sept. 26, 2014	Robert Mello, Ph.D.

The Chemistry Review for NDA 206-185

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Process and Facilities has issued an overall recommendation of Withhold for facilities. Therefore, from Product Quality perspective, this application is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Latanoprost is a prostaglandin analog used to reduce the intra ocular pressure. Latanoprost is an isopropyl ester pro-drug of latanoprost acid. The ester is hydrolyzed in-vivo to generate latanoprost acid, which is an agonist of prostanoid F2α receptor. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Latanoprost contains 5 chiral centers with the absolute chirality of 7-[(1R,2R,3R,5S)] and 2-[(3R)]. Latanoprost is a pale yellow to yellow viscous oil with a specific rotation [α] = 34.5°C (*c*=1, acetonitrile). It has a partition coefficient of 4.28 (cLogP) and a pKa of 14.84. It is freely soluble in many organic solvents such as acetone, ethanol, ethyl acetate, isopropanol, methanol, octanol and chloroform. However, it is practically insoluble in water and varying the pH between 1~12 do not affect its aqueous solubility.

Drug Product

Sun Pharma Advanced Research Company (SPARC) has developed a new formulation of latanoprost that is prepared as an emulsion in aqueous phase. The formulation has a different composition than the reference drug Xalatan®. The proposed drug product, Xelpros® is an emulsion composed of (b) (4) Water for Injection (WFI), boric acid, sodium borate, edentate disodium and potassium sorbate (b) (4) castor oil, latanoprost, and (b) (4)). Xelpros® is described as an off-white, translucent, isotonic, sterile emulsion. It is buffered to (b) (4) and is preserved using potassium sorbate, NF. As such, SPARC's formulation of latanoprost ophthalmic emulsion is not preserved with benzalkonium chloride (BAK) but with potassium sorbate which is in contrast to the RLD which uses BAK as preservative.

Furthermore, storage is recommended at (b) (4) unlike the RLD which is recommended to be stored at refrigerated condition.

Latanoprost ophthalmic emulsion, 0.005% w/v, 2.5 ml will be manufactured, processed, packaged, labeled and held by Sun Pharmaceutical Industries Ltd.–Halol, India. Testing to assure the identity, quality, purity and stability of the finish dosage form will be performed by Sun Pharmaceutical Industries Ltd. The intended commercial batch size and exhibit batch size for Latanoprost ophthalmic emulsion, 0.005%, w/v, 2.5 ml, is (b) (4) vials and (b) (4) bottles respectively. The drop size and drug content of each drop of the drug product, packaged in the selected primary packaging materials, is approximately (b) (4) µL and 1.51 µg, respectively.

B. Description of How the Drug Product is Intended to be Used

The recommended daily dose is one drop of the drug product. SPARC's latanoprost ophthalmic emulsion, 0.005%, is proposed for the same dosage (1 drop, 1.5 µg or 50 µg/mL) and administration (once daily in the evening) as that of the approved Reference Listed Drug (RLD) Xalatan®, for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Clinical studies indicate that SPARC latanoprost decreases IOP to levels similar to other marketed prostaglandin analogs approved for the reduction of elevated IOP.

This new formulation of latanoprost provides for storage stability that enables it to be stored at (b) (4) rather than at refrigerated temperatures of the RLD, Xalatan®. The change in formulation involves the introduction of a new excipient not previously used in an approved drug in the United States. The level of (b) (4) in SPARC's latanoprost formulation is low (b) (4). The applicant provided pharm-tox studies to qualify that (b) (4) does not cause direct ocular toxicity but does have the potential to cause sensitization reactions (Please refer to the Pharm/Tox review ; IND 102842). Please also note that the excipient (b) (4) (b) (4) is official in current USP37-NF32 Supplement 1.

SPARC is proposing a 24-month tentative expiration-dating period to be assigned to Latanoprost ophthalmic emulsion 0.005% w/v when stored at (b) (4). Based on the stability data provided this is acceptable. Computation of expiration date is done from the manufacturing date, and date of addition of active ingredient to the manufacturing process is designated as manufacturing date. The stability results show that the opening of the proposed container and use of the dropper does not affect the quality of the proposed drug product up to (b) (4) days.

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterile	Manufacturing	M	(b) (4)	Acceptable	Stability of

ophthalmic emulsion	process- (b) (4)		(b) (4)		emulsion; Monitor over release and stability
No Viscosity Test	Manufacturing process	L		Acceptable	Monitor over release and stability
No Particle size data	Manufacturing process	L		Acceptable	Monitor over release and stability
-	Product formulation	L		Acceptable	Compendial Quality
Identification	Drug Substance	L		Acceptable	Adequate DMF status

*Risk ranking applies to product attribute/CQA (L, M, H)
**For example, post marketing commitment, knowledge management post approval, etc.

C. Basis for Approvability or Not-Approval Recommendation

The proposed RLD is XALATAN® latanoprost ophthalmic solution, a sterile isotonic solution containing 50 μg/ml of latanoprost in a buffer solution of sodium chloride, sodium phosphates, water for injection and benzalkonium chloride as a preservative. The proposed drug product differs from the formulation of the RLD. XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005% w/v is an emulsion dosage form and includes as preservative potassium sorbate and normally stored (b) (4) (b) (4)

The SPARC latanoprost NDA application is a 505(b)(2) re-submission. SPARC has responded to outstanding comments of Review #1 included in the Complete Response letter of the original submission. The applicant was requested to update NDA with the correct dosage form of emulsion and revised acceptance criteria. The revised acceptance criteria are acceptable to ensure consistent drug product quality. Bioavailability information regarding product safety or effectiveness and waiver request has been provided in the NDA. The sponsor submitted a request for BA/BE waiver and was found acceptable based on the Biopharm review of Dr. Banu Zolnik (Oct. 17, 2014). Additionally, the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration (see review of Dr. Y. Zhang Clinical-Pharm dated

Sept.30,2014). SPARC conducted comparative, adequate, well controlled clinical trials in the U.S. (Study CLR_09_12 and Study CLR_09_13) to establish clinical efficacy and safety.

The Office of Process and Facilities has issued an overall withhold recommendation for facilities on this NDA (21CFR314.125(b)(13). Therefore, this application is not recommended for approval from Product Quality perspective.

III. Administrative

A. Reviewer's Signature

{See appended electronic signature page}

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D. Date: 20-July-2015

Branch Chief: Balajee Shanmguam, Ph.D. Date:

C. CC Block

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment 1: Facility Re-Evaluation Report- Withhold Recommendation

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications
Time run: 7/17/2015 12:10:31 PM

Facility FEI	Facility DUNS	Issue Name	Alert Type	Status	Entry Date	Entered By
3002809586	719638124	OAI/POAI Alert: SUN PHARMACEUTICAL INDUSTRIES LIMITED	Official Action Indicated	NEW	10/2/2014	DARRTS MIGRATION
3002809586	725959238	OAI/POAI Alert: SUN PHARMACEUTICAL INDUSTRIES LIMITED	Official Action Indicated	NEW	2/24/2015	DARRTS MIGRATION

Facility Status View for NDA 206185 Original 1

Displays information for the facilities that are associated to NDA 206185 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
Time run: 7/17/2015 12:10:32 PM

Overall Manufacturing Inspection Recommendations for NDA 206185 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Re-Evaluation Date	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 206185-Orig1-New/NDA(1)	SUN PHARMA ADVANCED RESEARCH CO LTD	Withhold	03/01/2015	Complete	11/13/2014
NDA 206185-Orig1-Resubmission/Class 2(18)	SUN PHARMA ADVANCED RESEARCH CO LTD	Withhold	09/30/2015	Complete	6/17/2015

OPF Facility Recommendations for Facilities on NDA 206185 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 206185-Orig1-Resubmission/Class 2(18)	3007512695	676162401	SUN PHARMA ADVANCED RESEARCH COMPANY LIMITED	CTL CONTROL TESTING LABORATORY	Approve Facility	07/31/2015	Complete	4/28/2015
NDA 206185-Orig1-Resubmission/Class 2(18)	(b) (4)			CTL CONTROL TESTING LABORATORY			Cancelled	5/12/2015
NDA 206185-Orig1-Resubmission/Class 2(18)				CTL CONTROL TESTING LABORATORY			Cancelled	4/28/2015
NDA 206185-Orig1-Resubmission/Class 2(18)				CTL CONTROL TESTING LABORATORY			Cancelled	4/28/2015

Data refreshed on: 07/17/15 08:37:01 AM

Milton J. Sloan -S

Digitally signed by Milton J. Sloan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300124000, cn=Milton J. Sloan -S
Date: 2015.07.27 14:34:45 -04'00'

Balajee Shanmugam -S

Digitally signed by Balajee Shanmugam -S
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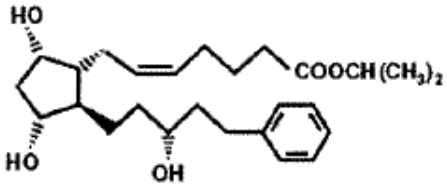
Date: 2015.07.27 15:24:49 -04'00'

NDA 206-185

XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005% w/v

Sun Pharma Advanced Research Company



Drug Product Reviewer: Milton J. Sloan, Ph.D.
Drug Substance Reviewer: Mariappan Chelliah, Ph.D.
.
ONDQA Pre-Marketing Assessment Division II Branch V

For Division of Transplant and Ophthalmology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-185

2. REVIEW #: 1

3. REVIEW DATE: 2-Oct-2014

4. REVIEWER: Milton J. Sloan, Ph.D.

Primary Review Team:

Reviewer	NDA Section
Mariappan Chelliah, Ph.D	Drug Substance: Lantanoprost, DMF
Milton Sloan, Ph.D.	Drug Product
Banu Zolnik, Ph.D.	Biopharmaceutics Review

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	NDA
Balajee Shanmugam, Ph.D.	NDA

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	31-Jan-2014
Amendment	09-July-2014
Amendment	30-Sept-2014

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Sun Pharma Advanced Research Company Limited
Address:	Tandalja, Vadodara, Gujarat, India 390020
Representative:	Aron Shapiro, Vice President, Ora, Inc. 300 Brickstone Square Andover, MA 01810
Telephone:	(978) 685-8900

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: XELPROS
b) Non-Proprietary Name (USAN): Latanoprost
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3,
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Prostaglandin analog

11. DOSAGE FORM: Ophthalmic emulsion

12. STRENGTH/POTENCY: 0.005% w/v (125µg/2.5mL)

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: _X__R_x ___OTC

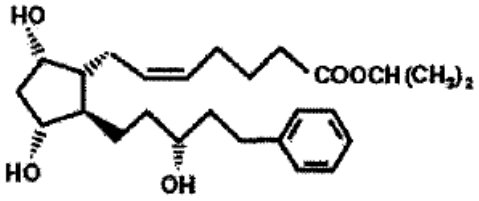
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name for Lantanoprost is: (5Z)-7-[(1R,2R,3R,5S)- 3,5-dihydroxy-2-[(3R)-3-hydroxy- 5-phenylpentyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester

Structural formula:



Molecular Formula: $C_{26}H_{40}O_5$
Molecular Weight: 432.61

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lantanoprost	1	Adequate	Reviewed by Dr, M. Chelliah (10/15/2014)	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	
(b) (4)	IV	(b) (4)		1	Adequate	Reviewed by Dr. J. Vidra (3/13/2014)	IR was sent to DMF holder.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-597	RLD
IND	102842	

18. STATUS:

ONDQA:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Recommendation is Pending-Potential OAI	Apr. 11, 2014	EES_PROD
Pharm/Tox	Acceptable		
Biopharm	Request for bioequivalence/bioavailability waiver acceptable	Oct. 17, 2014	Banu Zolnik, Ph.D.
LNC	N/A		
Methods Validation	Not requested per ONDQA policy		
DMEPA	Outstanding label comments	Sept. 12, 2014	Rachna Kapoor, Pharm.D.
EA	Request for Categorical Exclusion-Acceptable		Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	Sept. 26, 2014	Robert Mello, Ph.D.

The Chemistry Review for NDA 206-185

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance has not issued an acceptable recommendation on this NDA. Approval for this NDA is recommended only when all supporting sites have an acceptable recommendation. The applicant has been requested to update NDA with the correct dosage form of emulsion and the revised acceptance criteria. Also, with regards to the related CMC reviews and consults, the final review of the Biopharm (dated Oct 17, 2014)and Quality Microbiology (dated Sept. 26, 2014) recommend approval. DMEPA has outstanding label comments. Final labeling comments are still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Latanoprost is a prostaglandin analog used to reduce the intra ocular pressure. Latanoprost is an isopropyl ester pro-drug of latanoprost acid. The ester is hydrolyzed in-vivo to generate latanoprost acid, which is an agonist of prostanoid F2α receptor. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Latanoprost contains 5 chiral centers with the absolute chirality of 7-[(1R,2R,3R,5S)] and 2-[(3R)]. Latanoprost is a pale yellow to yellow viscous oil with a specific rotation [α] = 34.5°C (*c*=1, acetonitrile). It has a partition coefficient of 4.28 (cLogP) and a pKa of 14.84. It is freely soluble in many organic solvents such as acetone, ethanol, ethyl acetate, isopropanol, methanol, octanol and chloroform. However, it is practically insoluble in water and varying the pH between 1~12 do not affect its aqueous solubility.

Drug Product

Sun Pharma Advanced Research Company (SPARC) has developed a new formulation of latanoprost that is prepared as an emulsion (b) (4). The formulation has a different composition than the reference drug Xalatan . The proposed drug product,

Xelpros® is an emulsion composed of [redacted] Water for Injection (WFI), boric acid, sodium borate, edentate disodium, and potassium sorbate) and [redacted] ([redacted] castor oil, latanoprost, and [redacted]. Xelpros® is described as an off-white, translucent, isotonic, sterile emulsion. It is buffered to [redacted] and is preserved using potassium sorbate, NF. As such, SPARC's formulation of latanoprost ophthalmic emulsion is not preserved with benzalkonium chloride, in contrast to the RLD, and storage is recommended at [redacted].

Latanoprost ophthalmic emulsion, 0.005% w/v, 2.5 ml will be manufactured, processed, packaged, labeled and held by Sun Pharmaceutical Industries Ltd.–Halol. Testing to assure the identity, quality, purity and stability of the finish dosage form will be performed by Sun Pharmaceutical Industries Ltd.–Halol. The intended commercial batch size and exhibit batch size for Latanoprost ophthalmic emulsion, 0.005%, w/v, 2.5 ml, is [redacted] vials and [redacted] bottles respectively. The drop size and drug content of each drop of the drug product, packaged in the selected primary packaging materials, is approximately [redacted] µL and 1.51 µg, respectively.

B. Description of How the Drug Product is Intended to be Used

The recommended daily dose is one drop of the drug product. SPARC's latanoprost ophthalmic emulsion, 0.005%, is proposed for the same dosage (1 drop, 1.5 µg or 50 µg/mL) and administration (once daily in the evening) as that of the approved Reference Listed Drug (RLD) Xalatan®, for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Clinical studies indicate that SPARC latanoprost decreases IOP to levels similar to other marketed prostaglandin analogs approved for the reduction of elevated IOP.

This new formulation of latanoprost provides for storage stability that enables it to be stored at [redacted] rather than at refrigerated temperatures of the RLD, Xalatan®. The change in formulation involves the introduction of a new excipient not previously used in an approved drug in the United States. The level of [redacted] in SPARC's latanoprost formulation is low [redacted]). The applicant provided pharm-tox studies to qualify that [redacted] does not cause direct ocular toxicity but does have the potential to cause sensitization reactions (Please refer to the Pharm/Tox review ; IND 102842). Please also note that the excipient [redacted] is official in current USP37-NF32 Supplement 1.

SPARC is proposing a 24-month tentative expiration-dating period to be assigned to Latanoprost ophthalmic emulsion 0.005% w/v when stored [redacted]. Based on the stability data provided this acceptable. Computation of expiration date is done from the manufacturing date, and date of addition of active ingredient to the manufacturing process is designated as manufacturing date. The stability results show that the opening of the proposed container and use of the dropper does not affect the quality of the proposed drug product up to 45 days.

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterile ophthalmic emulsion	Manufacturing process- (b) (4)	M	(b) (4)	Acceptable	Stability of emulsion; Monitor over release and stability
No Viscosity Test	Manufacturing process	L		Acceptable	Monitor over release and stability
No Particle size data	Manufacturing process	L		Acceptable	Monitor over release and stability
-	Product formulation	L		Acceptable	Compendial Quality
Identification	Drug Substance	L		Acceptable	Adequate DMF status

*Risk ranking applies to product attribute/CQA (L, M, H)
**For example, post marketing commitment, knowledge management post approval, etc.

C. Basis for Approvability or Not-Approval Recommendation

The proposed RLD is XALATAN® latanoprost ophthalmic solution, a sterile isotonic solution containing 50 µg/ml of latanoprost in a buffer solution of sodium chloride, sodium phosphates, water for injection and benzalkonium chloride as a preservative. The proposed drug product differs from the formulation of the RLD. XELPROS™ (Latanoprost Ophthalmic emulsion) 0.005% w/v is an emulsion dosage form and includes as preservative potassium sorbate and normally stored (b) (4).
The SPARC latanoprost NDA application is a 505(b)(2) submittal. Bioavailability information regarding product safety or effectiveness and waiver request is provided in the NDA. The sponsor submitted a request for BA/BE waiver and was found acceptable based on the Biopharm review of Dr. Banu Zolnik (Oct. 17,2014). Additionally, the differences in formulation between Xalatan and the proposed SPARC latanoprost ophthalmic emulsion 0.005% are not expected to influence the limited systemic exposure to latanoprost/latanoprost acid following topical ocular administration (see review of Dr. Y. Zhang Clinical-Pharm dated Sept.30,2014).

SPARC conducted comparative, adequate, well controlled clinical trials in the U.S. (Study CLR_09_12 and Study CLR_09_13) to establish clinical efficacy and safety.

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance has not issued an acceptable recommendation on this NDA (21CFR314.125(b)(13).

III. Administrative

A. Reviewer's Signature

{See appended electronic signature page}

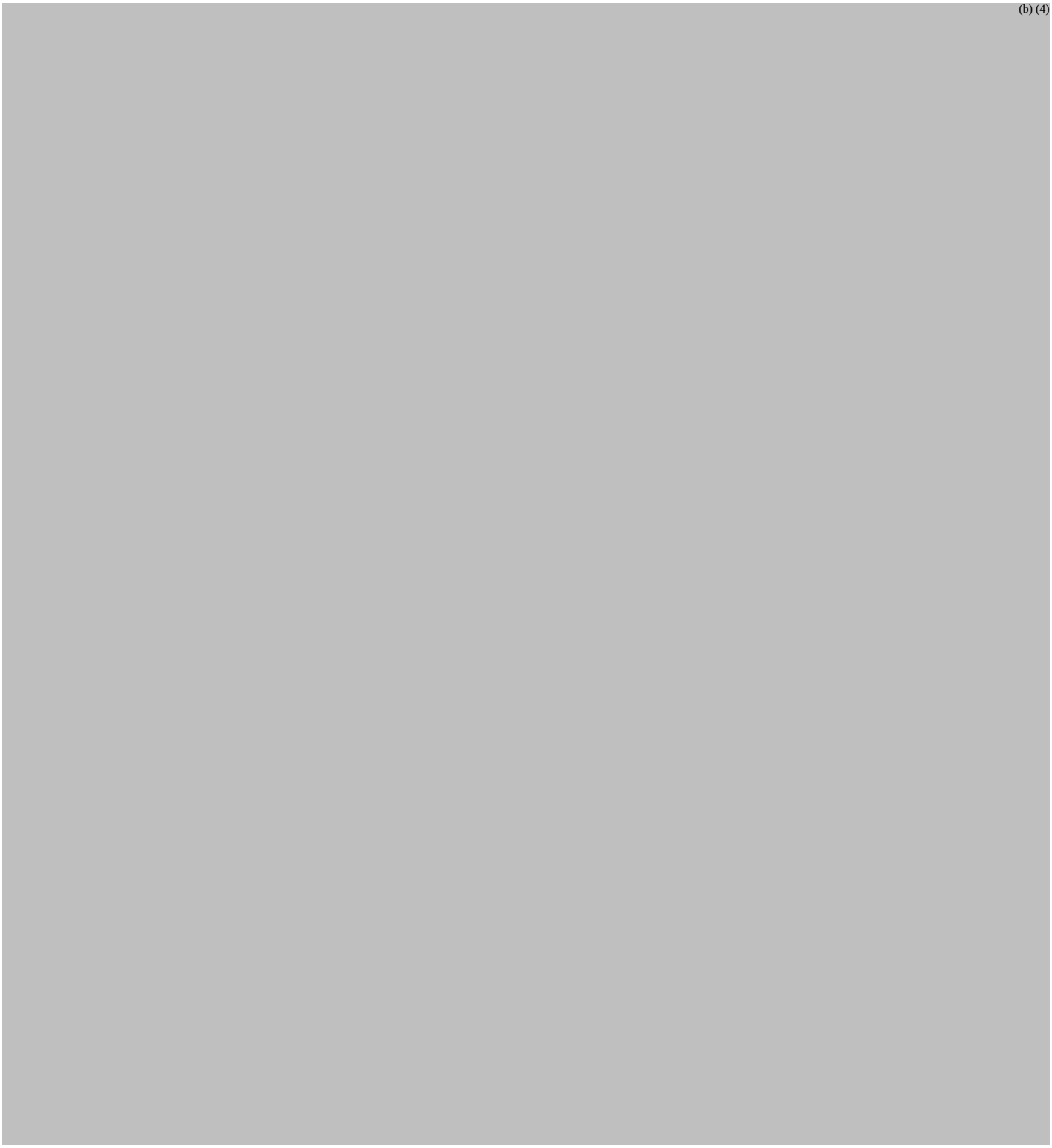
B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D.	Date: 06-March-14 Final Draft: 16-Oct-14
Branch Chief: Rapti Madurawe, Ph.D.	Date:

C. CC Block

68 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



Review Evaluation Comment:

SPARC has provided up to 36 months long term stability data that indicate all monitored attributes comply with the proposed stability specification. SPARC is

proposing a 24-month tentative expiration-dating period to be assigned to Latanoprost ophthalmic emulsion 0.005% w/v when stored at (b) (4) *and is acceptable. The computation of expiration date is done from the manufacturing date, and date of addition of active ingredient to the manufacturing process is designated as manufacturing date.*

A APPENDICES

A.1 Facilities and Equipment (biotech only)

Not applicable; not a biotech product.

A.2 Adventitious Agents Safety Evaluation

There is no potential for the contamination of the drug product with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents.
There is no potential for the contamination of the drug substance with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents. A declaration from the drug substance manufacturer is provided in Section 3.2.A.2, Attachment 1.

A.3 Novel Excipients

There are no novel excipients in the drug product.

R REGIONAL INFORMATION

R1 Executed Batch Records

R2 Comparability Protocols

Not applicable.

R3 Methods Validation Package

Review Comment:

The method validation package was not sent to FDA District laboratories per Office policy.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

(b) (4)

(b) (4)

[redacted]

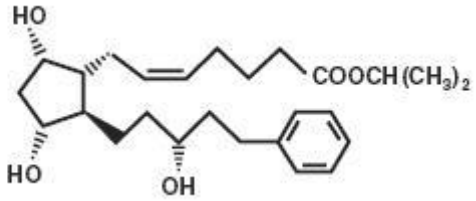
3 DOSAGE FORMS AND STRENGTHS

(b) (4) ophthalmic emulsion of latanoprost 0.005% (50 µg/mL).

11 DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:

M.W. 432.58



Latanoprost is a pale yellow to yellow viscous oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

XELPROS Sterile Ophthalmic Emulsion (latanoprost ophthalmic emulsion) is supplied as a sterile, isotonic, buffered aqueous emulsion of latanoprost with a pH approximately 7.0 and an osmolality of approximately 375mOsmol/kg. Each mL of XELPROS contains 50 micrograms of latanoprost. Potassium sorbate 0.47% is added as a preservative. The inactive ingredients are: castor oil, sodium borate, boric acid, propylene glycol, edetate disodium, polyoxyl 15 hydroxystearate, sodium hydroxide, hydrochloric acid, and water for injection. One drop contains approximately 1.5 µg of latanoprost.

16 HOW SUPPLIED/STORAGE AND HANDLING

XELPROS Ophthalmic emulsion is an off-white to pale yellow, translucent, isotonic, sterile, buffered emulsion of latanoprost 0.005% (50 µg/mL). It is supplied as a 2.5 mL emulsion in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, and a turquoise high density polyethylene pilfer-proof cap.

2.5 mL fill, 0.005% (50 µg/mL)

Package of 1 bottle NDC (b) (4)

Multi-Pack of 3 bottles NDC

Storage: Protect from light. Store (b) (4)

(b) (4)

Review Evaluation Comment:

There are currently outstanding comments for labeling from other review disciplines . Final review of the label is not possible at this time.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant requests a categorical exclusion from the preparation of an Environmental Impact Statement as provided under 21 CFR § 25.31(a).

III. List Of Deficiencies To Be Communicated

1. Please revise the (b) (4) (specified identified impurity) and highest unspecified impurity to NMT (b) (4)% for release and stability.
2. Please update the NDA submission to indicate the correct dosage form of emulsion and the revised acceptance criteria.

(IR dated 6/17/2014):

1. We note in your NDA submission you have referred to the dosage form as ophthalmic (b) (4), (b) (4). The proposed drug product is not a (b) (4) by definition and (b) (4) (b) (4). Please revise labeling to indicate ophthalmic emulsion dosage form, i.e., XELPROS (Latanoprost ophthalmic emulsion) 0.005%.

2. Please include the viscosity and particle size distribution of dispersed globules as CQAs (critical quality attributes) and monitor these over release and stability.

3. Determine the zeta-potential for the finished drug product.

4. Particle size unit appears to be mistyped in the submission. (See Tables 2.3.P.2-2, -3, 3.2.P.2.5.1.3, .4, .5, etc.).

5. Identification testing solely by retention time is not regarded as being specific. Per ICH Q6A you will need either two non-specific identification tests (e.g. two chromatographic procedures where separation is based on different principles or a single procedure with a combination of tests) or one specific test (e.g. infrared spectroscopy). Therefore, include a second test for identification. Provide the procedure of the test method and method validation.

6. Regulatory specifications apply over the shelf life of the drug product. Please combine finished drug product release and stability specifications into one table.

7. You have referred to impurities as "unknown", "highest unknown", and "known impurities" Please revise per ICH terminology, to (i.e., specified unidentified, specified identified, and unspecified).

8. Your acceptance criteria for the total impurities of NMT (b) (4)% is not justified based on the stability data provided. Please revise to NMT (b) (4)%.

9. We consider (b) (4) (b) (4) a novel excipient. It is neither listed in FDA's inactive ingredient database nor monographed in USP. Please list this excipient in Section P.4 of the NDA to be consistent with Module. 2.3.P.2.1.2.)

Attachment:

Attachment 1

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 206185/000	**Action Goal:**	
Stamp Date:	31-JAN-2014	**District Goal:**	01-OCT-2014
Regulatory:	30-NOV-2014		
Applicant:	SUN PHARMA ADV	**Brand Name:**	LATANOPROST 0.005% OPHTHALMIC (b) (4)
	300 BRICKSTONE SQ	**Estab. Name:**	
	ANDOVER, MA 01810	**Generic Name:**	LATANOPROST 0.005% OPHTHALMIC (b) (4)
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	590	001; (b) (4)	DROPS; LATANOPROST; 0.005%

Application Comment:

FDA Contacts:	M. SLOAN	Prod Qual Reviewer		3017961464
	R. MELLO	Micro Reviewer	(HFD-805)	3017961574
	N. BHANDARI	Product Quality PM		2404023815
	R. BLAY	Regulatory Project Mgr	(HFD-45)	3017963332

Overall Recommendation: PENDING on 21-FEB-2014 by EES_PROD

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Establishment Comment: RUG SUBSTANCE MANUFACTURER (on 21-FEB-2014 by N. BHANDARI () 2404023815)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	21-FEB-2014				BHANDARIN
OC RECOMMENDATION	30-JUL-2014			ACCEPTABLE	SAFAAIJAZIR

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611130 **FEI:** 3002809586

SUN PHARMACEUTICAL INDUSTRIES LTD.

HALOL-BARODA HWY HALOL-389350
HALOL, GUJARAT, INDIA

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURER, PACKAGING, RELEASE TESTING AND STABILITY TESTING.
DRUG SUBSTANCE ACCEPTANCE TESTING (on 03-FEB-2014 by N. BHANDARI () 2404023815)

Profile: STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS) **OAI Status:** POTENTIAL OAI

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	21-FEB-2014				BHANDARIN
SUBMITTED TO DO STERILE NO SLQ.	21-FEB-2014	10-Day Letter			WITTORFR
DO RECOMMENDATION	06-MAR-2014			ACCEPTABLE	PHILPYE
SUBMITTED TO DO	26-MAR-2014	Product Specific and GMP Inspection			SAFAAIJAZIR
NEW DOSAGE FOR ESTABLISHMENT - DO AC REC. PROVIDED BUT NO COMMENTS AS TO SLQ NOT BEING PROFILED. ALSO IT WILL BE MORE THAN 2 YRS SINCE LAST INSPECTION BY PDUFA GOAL DATE.					
ASSIGNED INSPECTION TO IB	11-APR-2014	Product Specific and GMP Inspection			PHILPYE

Milton J. Sloan -S

Digitally signed by Milton J. Sloan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300124000, cn=Milton J. Sloan -S
Date: 2014.10.24 09:36:53 -04'00'

Balajee Shanmugam -S

Digitally signed by Balajee Shanmugam -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217143, cn=Balajee Shanmugam -S
Date: 2014.10.24 09:41:48 -04'00'

Rapti D. Madurawe -A

Digitally signed by Rapti D. Madurawe -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300220251, cn=Rapti D. Madurawe -A
Date: 2014.10.24 11:51:17 -04'00'

BIOPHARMACEUTICS REVIEW **Office of New Drug Quality Assessment**			
Application No.:	NDA 206-185	**Reviewer:** Banu S. Zolnik, Ph.D.	
Division:	Division of Transplant and Ophthalmic Products		
Applicant:	Sun Pharma Advanced Research Company, Ltd.	**Biopharmaceutics Team Leader (Acting):** Okpo Eradiri, Ph.D.	
Trade Name:	Xelpros	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Latanoprost ophthalmic emulsion 0.005% w/v	**Date Assigned:**	2/5/2014
Indication	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	**Date of Review:**	10/17/2014
Formulation/ Strength	Emulsion, 0.005%	**Route of Administration**	Ophthalmic

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	**Date of informal/Formal Consult**	**Primary Review due in DARRTS**
Original dated 1/31/2014 eCTD seq. 008 dated 05/23/2014 eCTD seq. 011 dated 07/19/2014	NA	October 17, 2014
Type of Submission:	Original 505 (b)(2) Application	
Review Key Points:	▪ The evaluation of the biowaiver request	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission:
NDA 206185, Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v, 2.5 mL is a 505(b)(2) submission. Latanoprost is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Review:
The Biopharmaceutics review is focused on the evaluation and acceptability of the data and information supporting the biowaiver request.

Biowaiver request:

Based on 21 CFR § 320.22 (e), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore, the biowaiver request is granted. It is noted that this deferral is compatible with the protection of the public health.

RECOMMENDATION:
The ONDQA-Biopharmaceutics team has reviewed NDA 206185 and its amendments (Seq. 0008 and Seq.0014) submitted on May 23, and July 19, 2014. From the Biopharmaceutics perspective, NDA 206185 Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v is recommended for **APPROVAL.**

Banu S. Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Okpo Eradiri, Ph. D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

cc: P. Seo

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission

NDA 206185, Xelpros (latanoprost) ophthalmic emulsion, 0.005% w/v, 2.5 mL is a 505(b)(2) submission. Latanoprost is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

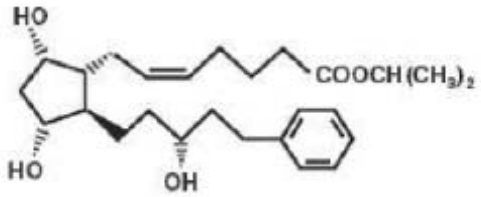
The listed drug, Xalatan® (NDA 20597, approval date June 5, 1996) is an isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and osmolality of approximately 267 mOsmol/kg.

In support of approval of Xelpros, the Applicant conducted four clinical studies: Study *CLR_09_12* (phase 3 safety and efficacy in the US), *CLR_09_13* (phase 3 safety in the US), *CLR_08_01* (phase 3 safety and efficacy in India), and *CLR_10_01* (pilot safety study in India).

Review

The Biopharmaceutics review is focused on the evaluation of the overall data supporting the approval of a waiver for the submission of an in vivo bioavailability/bioequivalence study.

Drug Substance



Latanoprost is pale yellow to yellow viscous oil. Very soluble in acetonitrile, freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, octanol, chloroform and practically insoluble in water.

Aqueous solubility (as a function of pH)

Solubility profile study of Latanoprost at different pH grades (1~12)

Solution	pH	Solubility(*)
Diluted HCL solution	1.0	Practically insoluble or Insoluble
Diluted HCL solution	4.0	Practically insoluble or Insoluble
Phosphate buffer solution	9.0	Practically insoluble or Insoluble
Phosphate buffer solution	12.0	Practically insoluble or Insoluble
(*) The result is justified according to current USP		

Drug Product

The proposed drug product is an off-white, translucent, sterile, isotonic (320-410 mOsm) emulsion formulation with a pH (b) (4) In the submission, the Applicant described the proposed formulation as a (b) (4) however during the review cycle it was determined that the proposed formulation is an emulsion (refer to CMC review for further information). The components of the proposed drug product are presented below.

The components, their function, and quality are provided in *Table 2.3.P.1-1*.

Table 2.3.P.1-1. Components of Latanoprost ophthalmic (b) (4) 0.005%				
Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	(b) (4)			NF
Edetate disodium				USP
Castor oil				USP
(b) (4)				Ph.Eur.
Propylene glycol				USP
Sodium borate				NF
Hydrochloric acid				NF
Sodium hydroxide				NF
Water for injection				USP
(b) (4)				

Following the determination of this product as an emulsion (refer to CMC review), the following biopharmaceutics comment was sent to the Applicant in IR letter dated 6/17/2014:

- **Since your proposed drug product is an emulsion, please provide a justification with sufficient/adequate data, including all the physical-chemistry control tests/methods supporting your reasons for not including the dissolution/drug release test in the specifications of the drug product.**

Reviewer's Assessment of Applicant's July 19, 2014 Response: SATISFACTORY

The Applicant stated that the proposed drug product contains castor oil (b) (4) dispersed in aqueous medium with he (b) (4) of the composition is very low. As a quality control, the Applicant accepted the CMC team recommendation to control the droplet size and included the droplet size as a control parameter in the finished product release (D10: between (b) (4) nm, D50: between (b) (4) nm, and D90: between (b) (4) nm.). The Applicant also provided physico-chemical properties such as pH, zeta potential, osmolality, % transmission, and surface tension for six different batches, and the parameters did not vary across the batches. The Applicant submitted l in vitro release study using dialysis tube on a bottle rotation apparatus (50 rpm) with 200 mL bottle with medium as the simulated tear fluid with 20% alcohol. Drug release profiles between different batches were evaluated using *f*2 analysis and show that drug release from different batches is similar to the clinical batch. Based on this information, and the Applicant's implementation of particle size, it is the reviewer's opinion that drug release specifications will not be needed.

Apparatus: Bottle rotating apparatus with 200 ml bottle.
Medium: Simulated tear fluid with 20% alcohol
Dialysis bag: Dialysis tube
Rpm: 50
Temperature: 37+/-0.5deg C
Time point: 0.5, 1,2, 4, 6, 8, 10, 12 h

Table 4: In-vitro release (%) study

Batch No$	Time points (h)						
	0.5	1	2	4	6	8	10
10712364SB036	27.3 ±3.87	41.6±4.60	64.9±5.73	86.5±4.20	97.8±2.88	102.3±1.68	104.7±1.14
JKJ1516	22.8±1.68	37.9±2.63	59.7±2.82	79.7±2.07	86.2±1.33	88.9±0.64	90.4±0.68
JKK0537	21.7±1.56	35.7±2.18	56.5±2.68	80.4±2.16	88.8±2.23	93.0±2.00	95.2±2.25
JKM3508	31.7±2.08	45.9±2.69	62.0±3.45	83.2±2.73	90.5±2.02	94.5±1.26	95.7±1.45
JKM3560	29.5±2.75	44.4±3.01	60.4±3.36	81.9±2.62	89.6±2.16	93.0±1.44	94.1±1.03
JKM4422	33.4±2.24	48.7±3.25	64.3±3.46	84.2±3.18	91.3±2.19	94.8±1.44	96.0±1.40

JKJ1516 clinical batch was taken as reference. $ See Mfg date from *Table 1*.

Table 5: Dis-similarity and similarity factor calculation of clinical batches# and other batches

Batch No$	Mean Particle size	F1	F2
JKJ1516#	(b) (4)	-	-
JKK0537		3.7	77.8
JKM3508		8.7	61.1
JKM3560		6.3	66.9
JKM4422		11.1	56.3
10712364SB036		11.1	57.7

JKJ1516 clinical batch was taken as reference. $ See mfg date from *Table 1*.

Biowaiver request:

The biopharmaceutics comment below was conveyed to the Applicant in the 74-day letter dated April 9, 2014

- **A request to waive the requirement for the submission of evidence measuring the in vivo bioavailability (BA) or bioequivalence (BE) of your proposed product is not included in your NDA. Please submit the BA/BE waiver request with supporting data.**

Reviewer's Assessment of Applicant's May 23, 2014 Response: SATISFACTORY

The Applicant stated that latanoprost is a highly permeable drug with extremely low systemic absorption and exposure following topical ophthalmic administration. The Applicant submitted comparative tissue distribution and PK data for the proposed drug product versus Xalatan in Male NZW Rabbits. In this non-clinical study, it is shown that maximum concentration of latanoprost in plasma was reached at 0.25 hour post dose and at around 4 hour time point latanoprost levels in plasma were below LOQs. Therefore, it was concluded that there was no significant systemic exposure to latanoprost following ocular administration in rabbits.

It is the ONDQA-Biopharmaceutics team's view that the proposed product is an ophthalmic emulsion, intended only for local therapeutic effect and its lack of systemic absorption, per 21 CFR § 320.22 (e), for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived and this deferral is compatible with the protection of the public health.

RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments**
In vitro release	The product is an emulsion formulation	L	(b) (4)	Acceptable	Control of the (b) (4)

* Risk ranking applies to product attribute/CQA (L, M, H)

Banu S. Zolnik -S

Digitally signed by Banu S. Zolnik -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Banu S. Zolnik -S, 0.9.2342.19200300.100.1.1=1300438310
Date: 2014.10.17 10:43:44 -04'00'

{See appended electronic signature page}
Banu S. Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Okponanabofa Eradiri, Ph.D.

Digitally signed by Okponanabofa Eradiri, Ph.D.
DN: cn=Okponanabofa Eradiri, Ph.D., o=ONDQA, ou=Biopharmaceutics, email=okpo.eradiri@fda.hhs.gov, c=US
Date: 2014.10.17 10:56:43 -04'00'

{See appended electronic signature page}
Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

Product Quality Microbiology Review

26 September 2014

NDA: **206-185**

Drug Product Name
Proprietary: XELPROS
Non-proprietary: Latanoprost ophthalmic emulsion 0.005%w/v

Review Number: **1**

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
31 January 2014	31 January 2014	31 January 2014	07 February 2014
09 July 2014	09 July 2014	n/a	n/a

Submission History (for 2nd Reviews or higher): N/A

Applicant/Sponsor
Name: Sun Pharma Advanced Research Co., Ltd
Address: Tandalja, Vadodara,
Gujarat 390020
INDIA
Representative: Aron Shapiro, Vice President, Ora, Inc.
(Authorized Representative)
300 Brickstone Square
Andover, MA 01810
Telephone: (978) 685-8900

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing authorization

3. MANUFACTURING SITE: Sun Pharmaceutical Industries Ltd.
Halol-Baroda Highway
Halol-389350
Gujarat, INDIA
FEI: 3002809586

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Ophthalmic emulsion; topical 0.005% w/v, packaged 2.5 mL in a 5 mL LDPE sterile dropper bottle, stoppered (b) (4) and closed with HDPE cap.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Reduction of intra-ocular pressure in Glaucoma/ocular hypertension

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: None.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

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

(b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. 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[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	10		5	5	250	Simulations and interventions conducted during media fills, Environmental monitoring
Endo		4		4	4	64	

(b) (4)

(b) (4)

6 = RPN = O (after modification when applicable) ×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

Initial Risk Assessment – RPN = 250 High risk for sterility
RPN = 64 Moderate risk for endotoxins

B. Final Risk Assessment - The Applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility and pyrogenicity risks to the final drug product. (b) (4) There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product. The drug product is preserved and adequate preservative effectiveness testing was conducted during development. This testing is also a part of the long term stability program.

III. Administrative

A. Reviewer's Signature _____
Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block _____
Neal J. Sweeney, Ph.D.
Senior Microbiology Reviewer

C. CC Block: NDA 206-185

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 is not sterile. No review is performed here. It is noted that there are microbial limit controls on the drug substance.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product START HERE

- Description of drug product – The drug product is an off-white/pale yellow, translucent, isotonic, sterile [redacted] that is preserved with 0.47% w/v potassium sorbate.
- Drug product composition – See Table 3.2.P.1-1 "*Components of Latanoprost ophthalmic [redacted] 0.005%"* below, (copied from submission section 3.2.P.1 page 1/1).

Table 3.2.P.1-1. Components of Latanoprost ophthalmic [redacted] 0.005%

Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	[redacted]			NF
Edetate disodium				USP
Castor oil				USP
[redacted]				Ph.Eur.
Propylene glycol				USP
Sodium borate				NF
Hydrochloric acid				NF
Sodium hydroxide				NF
Water for injection				USP
[redacted]				

- Description of container closure system – The drug product is packaged as a 2.5mL [redacted] in a multiple-use 5mL [redacted] low-density polyethylene bottle (LDPE dropper bottle, [redacted]) having a [redacted] LDPE dropper tip and a [redacted] turquoise ([redacted]) opaque, high density polyethylene (HDPE) [redacted] screw cap.

P.2 Pharmaceutical Development

[redacted]

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(b) (4)

- ADEQUATE -

REVIEWER COMMENT – The Applicant has provided an adequate long term stability program to assess the microbial quality of the commercial drug product over the life of the product.

R REGIONAL INFORMATION

R.1 **Executed Batch Record**: The Applicant submitted a representative executed batch manufacturing record for batch # JK82671. This record was used during the course of this review to substantiate various manufacturing processes described in the narrative text of the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. **PACKAGE INSERT**: The Applicant submitted draft labelling text for the drug product. Review of this draft text from a microbiological perspective did not reveal any significant issues.

- ADEQUATE -

REVIEWER COMMENT – Storage conditions are consistent with the long term stability program. There are no microbiological issues related to the labeling.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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

/s/

ROBERT J MELLO
09/26/2014

NEAL J SWEENEY
09/26/2014
I concur.