CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208073Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208073
Review # 2

May 2nd, 2016

Drug Name/Dosage Form	Xiidra (Lifitegrast ophthalmic solution)5%
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	Jan 22, 2016
Amendment	Mar 14, 2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	OPQ/ONDP/DNDAPI/NDBI
Drug Product	Shrikant Pagay	OPQ/ONDP/DNDPI/NDPBIII
Process	Edwin jao	OPQ/OPF/DPAIII/PABVII
Microbiology	Denise Miller	OPQ/OPF/DMA/MABII
Facility	Frank Wackes	OPQ/OPF/DIA/IABII
Biopharmaceutics	Elsbeth Chikhale	OPQ/ONDP/DB/BBI
Regulatory Business Process Manager	Erin Andrews	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	OPQ/ONDP/DNDPI/NDPBIII
Laboratory (OTR)	NA	NA
ORA Lead	Paule Perdue	OGROP/ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

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Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Quality micro and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1 dated on Jul 28, 2015. As documented in this resubmission Review #2, all Complete Response issues including drug substance, drug product and process have been satisfactorily resolved. The Office of Process and Facilities (OPF) has provided an overall recommendation of "acceptable" for the facilities on Feb 26, 2016. Therefore, NDA 208073 is recommended for approval from Product Quality perspective.

CMC-related labeling recommendations have been provided to the OND PM for consideration during final labeling discussions.

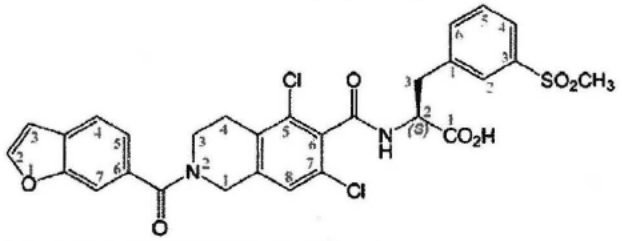
1. Summary of Complete Response issues: Not Applicable
2. Action letter language, related to critical issues such as expiration date: "An expiration dating period of 18-months is granted for Lifitegrast ophthalmic solution, 5% when packaged and stored as described in the attached labeling."
3. Benefit/Risk Considerations:
   Evaluation of the quality aspects of Lifitegrast ophthalmic solution, 5% supports approval without consideration of specific benefit/risk aspects.

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

1. Chemical Name or IUPAC Name/Structure
   This is a new molecular entity (NME).



(*S*)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid
Chemical Formula: $C_{29}H_{24}Cl_2N_2O_7S$
Molecular Weight: 615.48

2. Properties/CQAs Relevant to Drug Product Quality
   The CQA relevant to drug product quality are solubility at pH 7.0 – 8.0 and stability in solution.

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(b) (4)

[redacted]

B. Drug Product [Established Name] Quality Summary

1. Strength
   Ophthalmic Solution, 5%

2. Description/Commercial Image
   The drug product is a clear, colorless to slightly colored sterile ophthalmic solution filled in LDPE unit dose (b) (4). The commercial presentation will provide five (b) (4) placed in a (b) (4) foil pack.

3. Summary of Product Design
   In the early development, the product was (b) (4) were removed from the formulation as the product was converted to a single dose container. (b) (4) The batch size for the commercial product is approximately (b) (4).

4. List of Excipients
   Sodium chloride (b) (4) sodium phosphate dibasic anhydrous (b) (4) sodium thiosulfate pentahydrate (b) (4) sodium hydroxide

(pH adjuster), hydrochloric acid (pH adjuster), and water for injection (b) (4).

5. Process Selection (Unit Operations Summary)
   a. Sterilization processes of the drug product, as applicable

(b) (4)

6. Container Closure
   The primary container closure for the ophthalmic solution is a single dose (b) (4) low density polyethylene (LDPE) (b) (4) manufactured using the (b) (4). The target fill volume is (b) (4). Five (b) (4) are packaged in a (b) (4) foil.

7. Expiration Date & Storage Conditions
   The applicant is proposing a shelf life of (b) (4) months when stored at 20-25°C (68-77°F). Based on the review of available data, a shelf life of 18 months can be granted at this time.

8. List of co-packaged components
   None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xiidra
Non Proprietary Name of the Drug Product	Lifitegrast Ophthalmic Solution, 5%
Non Proprietary Name of the Drug Substance	Lifitegrast
Proposed Indication(s) including Intended Patient Population	Treatment of signs and symptoms of dry eye disease
Duration of Treatment	Not applicable
Maximum Daily Dose	One drop of Xiidra in each eye, twice a day
Alternative Methods of Administration	Not applicable

D. Biopharmaceutics Considerations

1. BCS Classification: Not requested

- Drug Substance:
- Drug Product:

2. Biowaivers/Biostudies
   - Biowaiver Requests: Granted
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

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

Chunchun Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137
Date: 2016.05.02 10:47:50 -04'00'

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

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ASSESSMENT OF THE FACILITIES

The Office of Process and Facilities (OPF) has provided an overall recommendation of "acceptable" for the facilities in the Panorama by Frank Wackes on Feb 26, 2016.

ASSESSMENT OF THE BIOPHARMACUETICS

Recommended for approval, see Review #1.

ASSESSMENT OF MICROBIOLOGY

Recommended for approval, see Review #1.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Recommended for approval, see Review #1.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

XIIDRA™ (lifitegrast ophthalmic solution) 5%

Ophthalmic solution containing lifitegrast 5% (50 mg/mL).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Yes	Establishment changed (b) (4) (b) (4) to (lifitegrast ophthalmic solution)
Dosage form, route of administration	Yes	Concur
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Yes	concur

Conclusion:
Acceptable after established name has been revised (b) (4) to (lifitegrast ophthalmic solution).

(b) "Full Prescribing Information" Section

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

Ophthalmic solution containing lifitegrast 5% (50 mg/mL)

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

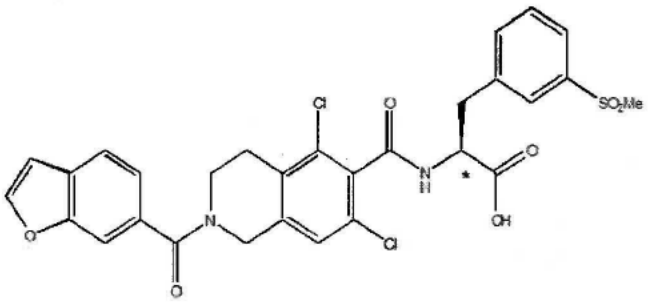
Conclusion: Acceptable

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

11 DESCRIPTION

The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. The molecular formula of lifitegrast is $C_{29}H_{24}Cl_2N_2O_7S$ and its molecular weight is 615.5. The structural formula of lifitegrast is:

* Chiral center



* Chiral center

Lifitegrast is a white to off-white powder which is soluble in water.

Xiidra (lifitegrast ophthalmic solution) 5% is supplied as a sterile clear, colorless to slightly colored isotonic solution with a pH range of 7.0–8.0 and with an osmolality range of 200–330 mOsmol/kg.

Xiidra contains **Active:** lifitegrast 50 mg/mL; **Inactives**: sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	yes	concur
Dosage form and route of administration	yes	concur
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA	concur
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	yes	concur
Statement of being sterile (if applicable)	yes	concur
Pharmacological/ therapeutic class	Provided in section 1	concur
Chemical name, structural formula, molecular weight	yes	concur
If radioactive, statement of important nuclear characteristics.	NA	concur
Other important chemical or physical properties (such as pKa, solubility, or pH)	yes	concur

Conclusion: Adequate with the proposed changes highlighted.

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

Xiidra (lifitegrast ophthalmic solution) 5% is supplied in foil pouch containing 5 low density polyethylene 0.2 mL single-use containers.

NDC 54092-606-01; Carton of 60 single-use containers.

Storage:

Store at 20-25°C (68-77°F), Store single-use containers in the original foil pouch.

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

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)	yes	concur

Conclusion: satisfactory after the recommended highlighted changes.

2. Container and Carton Labeling

1) Immediate Container Label

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

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

3) *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.
4) **For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

5) **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.

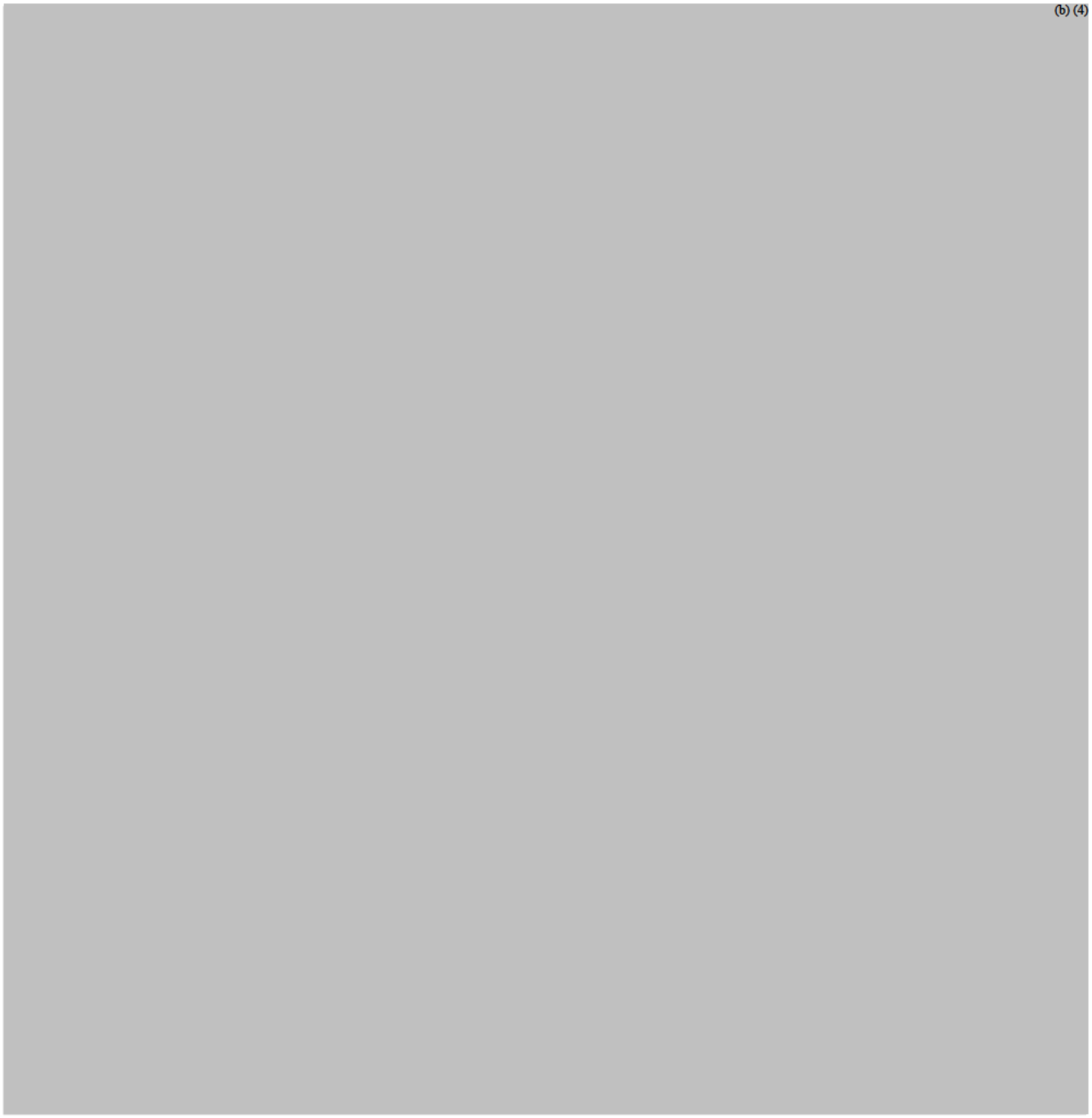
6)

Conclusion: Adequate with the storage temperature revised as follows:
The Storage conditions should be revised to read, 'Store at 20-25°C (68-77°F). Store single-use containers in the original foil pouch."
This information needs to be revised on the container label.

7) Carton Labeling

(b) (4)

(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))	Yes; however for establishment name change (b) (4) (b) (4) to (lifitegrast Ophthalmic solution) 5%	Concur with changes
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	yes	concur
Net contents (21 CFR 201.51(a))	yes	concur
Lot number per 21 CFR 201.18	yes	concur
Expiration date per 21 CFR 201.17	yes	concur
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	yes	**concur**
Sterility Information (if applicable)	Included on the container; not on the carton	**concur**
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	yes	concur
Storage Conditions	yes	concur
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	concur
Bar Code per 21 CFR 201.25(c)(2)**	yes	concur
Name of manufacturer/distributor	yes	concur
"See package insert for dosage information" (21 CFR 201.55)	yes	concur
"Keep out of reach of children" (optional for Rx, required for OTC)	NA	**concur**
Route of Administration (not	yes	**concur**

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Adequate with the proposed changes listed below for Carton for a 60 single use Trade package and for a 20 single use Physician's sample package

- *Usual Dosage should be revised to read: "Place one drop twice a day in each eye. Use one single-use container immediately after opening and then discard."*
- *The Storage conditions should be revised to read, 'Store at 20-25°C (68-77°F). Store single-use containers in the original foil pouch." The language concerning* (b) (4) *should be deleted.*
- *The established name should read: (lifitegrast ophthalmic solution) 5%*

The above information needs to be revised on the carton label.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: CMC portion os the label is revised. The CMC portion of the label is adequate for the NDA.

Shrikant N.Pagay, May 1st, 2016

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., Division of New Drug Products I.
May 2, 2016

Expedited Review

Recommendation:
NDA: Complete Response.

NDA 208073
Review #1 Addendum
Review Date September 25, 2015

Drug Name/Dosage Form	Xiidra (Lifitegrast 5.0% Ophthalmic Solution)
Strength	5.0%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	February 25, 2015
Amendment	March 25, 2015
Amendment	June 10, 2015
Amendment	June 16, 2015
Amendment	June 18, 2015
Amendment	July 20, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	OPQ/ONDP/DNDAPI/NDBI
Drug Product	Shrikant Pagay	OPQ/ONDP/DNDPI/NDPBIII
Process	Edwin Jao	OPQ/OPF/DPAIII/PABVII
Microbiology	Yuansha Chen	OPQ/OPF/DMA/MABII
Facility	Frank Wackes	OPQ/OPF/DIA/IABII
Biopharmaceutics	Elsbeth Chikhale	OPQ/ONDP/DB/BBI
Project/Business Process Manager	Navi Bhandari	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Anamitro Banerjee	OPQ/ONDP/DNDPI/NDPBIII
Laboratory (OTR)	-	-
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

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Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is NOT recommended for approval from the CMC perspective.
The deficiencies to be communicated to the applicant are rephrased from Review 1 for clarity (see page12). Redundant minor comments were removed.

1. Summary of Complete Response issues
   This application is not recommended for approval at this time. The following issues should be addressed by the applicant.
   Drug Substance: The acceptance criteria for (b) (4) should be tightened. As the proposed acceptance limit for (b) (4) is not acceptable, the (b) (4) provision for testing this impurity should be removed.
   Drug Product: Specifications for leachables are not acceptable.
   Process: The reconciliation table in the amendment dated June 10, 2015 is unclear, incomplete, and inaccurate. Recommendations are made to correct this table.

2. Action letter language, related to critical issues such as expiration date
   CMC information provided in this NDA is inadequate.

3. Benefit/Risk Considerations
   None

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

1. Chemical Name or IUPAC Name/Structure

This is a new molecular entity (NME).

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(b) (4)

[redacted]

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xiidra
Non Proprietary Name of the Drug Product	Lifitegrast 5.0% Ophthalmic Solution
Non Proprietary Name of the Drug Substance	Lifitegrast
Proposed Indication(s) including Intended Patient Population	Treatment of signs and symptoms of dry eye disease
Duration of Treatment	Not applicable
Maximum Daily Dose	One drop of Xiidra in each eye, twice a day
Alternative Methods of Administration	Not applicable

D. Biopharmaceutics Considerations

1. BCS Designation: Not requested
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies
   - Biowaiver Requests: Granted

- PK studies: N/A
- IVIVC: N/A

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable.

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert
Pending

II. List of Deficiencies To Be Communicated

A. Complete Response Comments:

- Regarding your response to the Information Request dated June 2, 2015, we still believe that there is no adequate safety information to support the drug substance specification limit of (b)(4) ppm for (b)(4). Since no detectable levels of (b)(4) were present in the late-stage process batches tested to date (detection limit of (b)(4) ppm), revise the acceptance limit to "less than (b)(4) ppm."
- The (b)(4) provision for (b)(4) is not acceptable at this time. Removal of the test for (b)(4) may be requested once adequate data is available.
- In the leachable analysis in the stability study you have indicated that most of the impurities are degradants from the drug product and hence are not tracked in the leachables study. Provide evidence that these impurities originate from the drug product. Identify and qualify (i.e. provide safety data) the remaining unknown impurities that you identify as leachables.

B. Other Comments

- In the Amendment dated 16-Jun-2015, you provided the method validation report for *Assay, Purity, Impurities, and Identification Test by HPLC (Test Method TM.2975)*. The (b)(4) does not appear to give (b)(4) (b)(4) (b)(4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. Optimize the method (b)(4) (b)(4) for all potential degradation pathways or develop a new method that is stability-indicating.

- The Comparability Protocol included in the submission is not acceptable.

- The reconciliation table submitted in your amendment dated 6/10/2015 (table 1 of question 10) is unclear, incomplete, and inaccurate. Consider the following

recommendations when you revise the reconciliation table and/or submit any new tables.

- The table should contain acceptance criteria for actual yield (minimum and maximum of the corresponding theoretical yield) for each phase of production as per CFR211.186(b)(7).
- Provide definitions of the items listed in the first left column of the table, and indicate how they are calculated.
- Waste/loss/rejects during manufacturing should be indicated for each step with proper explanation.
- The actual yield for formulation (b) (4) should be the amount of solution available for filling plus that used for sampling, excluding any waste/loss.
- Provide the actual and theoretical yield for packaging. The actual yield for this step should be (b) (4)
- The reported (b) (4) is incorrect. It should be (b) (4) ".

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IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: Anamitro Banerjee/September 25, 2015
Secondary Reviewer Name/Date:
Project Manager Name/Date: Navi Bhandari

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: 2015.09.25 13:56:44 -04'00'

Expedited Review

Recommendation:
NDA: Complete Response.

NDA 208073
Review #1
Review Date July 28, 2015

Drug Name/Dosage Form	Xiidra (Lifitegrast 5.0% Ophthalmic Solution)
Strength	5.0%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	February 25, 2015
Amendment	March 25, 2015
Amendment	June 10, 2015
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Application Technical Lead	Anamitro Banerjee	OPQ/ONDP/DNDPI/NDPBIII
Laboratory (OTR)	-	-
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

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Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION:**

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
	Type II	-	-	-	-	-
(b) (4)	Type III *(if applicable)*					
	Type IV *(if applicable)*	-				
	Other	-				

[1] 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)

** DMF's (b) (4)) were not reviewed since sufficient information for the (b) (4) from the 2 suppliers and foi (b) (4) composition, specification, leachable /extractable data and statement about the compliance with the regulations were provided in the NDA.*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	077885	Lifitegrast developed by SARcode Biosciences (acquired by Shire)

3. **CONSULTS:**

No consults requested

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is NOT recommended for approval from the CMC perspective.

1. Summary of Complete Response issues
   This application is not recommended for approval at this time. The following issues should be addressed by the applicant.
   Drug Substance: The acceptance criteria for [redacted] (b) (4) should be tightened. As the proposed acceptance limit for [redacted] (b) (4) is not acceptable, the [redacted] (b) (4) for testing this impurity should be removed.
   Drug Product: Specifications for leachables are not acceptable.
   Process: The reconciliation table in the amendment dated June 10, 2015 is unclear, incomplete, and inaccurate. Recommendations are made to correct this table.

2. Action letter language, related to critical issues such as expiration date
   CMC information provided in this NDA is inadequate.

3. Benefit/Risk Considerations
   None

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

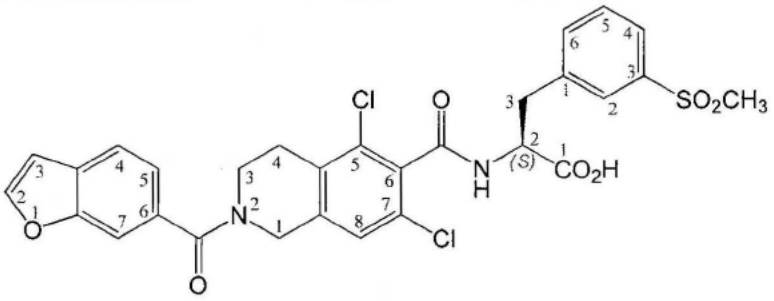
None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure

This is a new molecular entity (NME).



(*S*)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid

Chemical Formula: $C_{29}H_{24}Cl_2N_2O_7S$

Molecular Weight: 615.48

2. Properties/CQAs Relevant to Drug Product Quality

The CQA relevant to drug product quality are solubility at pH 7.0 – 8.0 and stability in solution.

3. List of starting materials

(b) (4)

[redacted]

(b) (4)

[redacted]

B. Drug Product [Established Name] Quality Summary

1. Strength

5.0% Ophthalmic Solution

2. Description/Commercial Image

The drug product is a clear, colorless to slightly colored sterile ophthalmic solution filled in LDPE (b) (4). The commercial presentation will provide five (b) (4) placed in a (b) (4) foil pack.

3. Summary of Product Design

In early development, the product was (b) (4) were removed from the formulation as the product was converted to a single dose container. (b) (4) (b) (4) The batch size for the commercial product is approximately (b) (4)

4. List of Excipients:

Sodium chloride (b) (4) sodium phosphate dibasic anhydrous (b) (4) sodium thiosulfate pentahydrate (b) (4) sodium hydroxide (pH adjuster), hydrochloric acid (pH adjuster), and water for injection (b) (4).

5. Process Selection (Unit Operations Summary)

(b) (4)

6. Container Closure

The primary container closure for the ophthalmic solution is a single dose (b) (4) low density polyethylene (LDPE) (b) (4) manufactured using the (b) (4). The target fill volume is (b) (4). Five (b) (4) are packaged in a (b) (4) foil.

7. Expiration Date & Storage Conditions

The applicant is proposing a shelf life of (b) (4) months when stored at 25°C (77°F) (b) (4) Based on the review of available data, a shelf life of (b) (4) months may be granted at this time.

8. List of co-packaged components

None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xiidra
Non Proprietary Name of the Drug Product	Lifitegrast 5.0% Ophthalmic Solution
Non Proprietary Name of the Drug Substance	Lifitegrast
Proposed Indication(s) including Intended Patient Population	Treatment of signs and symptoms of dry eye disease
Duration of Treatment	Not applicable
Maximum Daily Dose	One drop of Xiidra in each eye, twice a day
Alternative Methods of Administration	Not applicable

D. Biopharmaceutics Considerations

1. BCS Designation: Not requested
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies

- Biowaiver Requests: Granted
- PK studies: N/A
- IVIVC: N/A

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

I. Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable.

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: 2015.07.28 20:21:25 -04'00'

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33. **Are the in-vitro dissolution method and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

➢ ***Dissolution Test:***

The proposed drug product is a sterile, non-preserved, isotonic ophthalmic solution, containing lifitegrast (50 mg/mL), intended to be administered twice daily as a single drop to the ocular surface. Since the drug is already in solution, dissolution specifications (test and acceptance criteria) are not applicable for this drug product.

➢ ***Bioavailability:***

The proposed drug product is intended to act locally in the eye. A Phase 1 study in healthy subjects (Study SAR1118-001) showed that the overall plasma pharmacokinetic profile of lifitegrast demonstrated no systemic accumulation of topically administered lifitegrast with time, and lifitegrast plasma concentrations typically decreased rapidly to below measureable levels by 1 hour after administration.

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

➢ ***Formulation Bridging:***

Different drug product formulations were used during the development of this drug product in the Phase 2 studies, the first Phase 3 study (OPUS-1, study 1118-KCS-200), and the remaining Phase 3 studies (OPUS-2, study 1118-DRY-300; SONATA, study 118-DRY-400; and OPUS-3, study SHP606-304: which used the intended to-be-marketed (TBM) drug product). The difference between the two formulations used in the Phase 3 studies (last two columns in Table below) lies in the removal of (b) (4) from the later Phase 3 and TBM formulation.

Component	Phase 2 Formulation Composition (mg/mL)	OPUS-1 Formulation Composition (mg/mL)	OPUS-2/SONATA (Intended to Commercialize) Formulation Composition (mg/mL) [a]
Lifitegrast	50.0	50.0	50.0
(b) (4)			(b) (4)
Sodium thiosulfate, pentahydrate			
(b) (4)			
Sodium phosphate, dibasic, anhydrous			
(b) (4)			
Sodium chloride			
Sodium hydroxide (b) (4) hydrochloric acid			
Sterile water for injection			
			(b) (4)

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34.1. **Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?**

➢ ***Biowaiver Request:***

Section 1.12.15 of the NDA contains a request for a waiver of the CFR's requirement to submit in vivo bioavailability or bioequivalence studies to support the bridging of the various formulations used throughout product's development. The only quality attributes of the finished drug product that changed by a perceivable amount over the course of the clinical program were osmolality and individual and total impurities; neither of which affected the safety outcomes.

The osmolality range of the Phase 2 (batch# 03909E) and OPUS-1 formulations (batch# IGC6) was slightly higher (290-300 mOsm/kg), when compared to that of the drug product batches that were manufactured using the intended commercial formulation, including the OPUS-2/SONATA clinical supply batches (batch# 2F11) for which the osmolality range is 240-250 mOsm/kg.

Individual impurities of up to approximately (b) (4)% and total impurities of up to approximately (b) (4)% were reported for the Phase 2 clinical supply batches; while the impurities in the OPUS-2/SONATA clinical supply batches were below the limit of detection. All other measured quality attributes of the finished drug product solutions used in Phase 2 and Phase 3 clinical studies were comparable, as shown in the Table below.

BEST AVAILABLE COPY

Test	Proposed Acceptance Criteria*	Batch Number		
		03909E	IGC6	2F11
Appearance	Clear, colorless to slightly colored solution	(b) (4)		
Color	(b) (4)			
pH	7.0-8.0			
Osmolality	260-340 mOsm/kg			
Lidocaine Assay	(b) (4) % of Label Claim			
Degradation Products				
Any Individual Impurity	Not More Than (b) (4) %			
Total Impurities	Not More Than (b) (4) %			
Identification A: HPLC Retention Time	The retention time of the major peak of the sample corresponds to the Lidocaine peak in the reference standard solution.			
Identification B: UV Spectrum	Sample and reference standard HPLC peaks exhibit the same UV absorption spectra from 200-400nm			
Minimum Fill Volume				
Mean content	Not less than (b) (4) mL			
Content of any Single Container	Not less than (b) (4) mL			
Sodium Thiosulfate Assay	(b) (4) % of Label Claim			
Particulate Matter	Not More Than (b) (4)			
	Not More (b) (4)			
Sterility	No growth after (b) (4) days			
Endotoxin	Not more than (b) (4)			

The biowaiver request is also supported by the information generated in Study L6776M-SHP606, entitled "*Ocular Distribution and Pharmacokinetics of SSP-005493X (Lifitegrast) Following a Repeated Topical Ocular Dose Regimen to Pigmented Rabbits (see Module 2.6.4.3.1)*", which compared the ocular distribution of two lifitegrast formulations (formulation IGC6 used in OPUS-1 and formulation 2F11 used in OPUS 2 and SONATA) in pigmented rabbits.

In study L6776M-SHP606, the distribution of lifitegrast was evaluated in ocular tissues following instillation of 1.75 mg/eye (comparable to 5.0% clinical dose) twice daily approximately 12 hours apart for 5 consecutive days. The exposure was highest in the conjunctiva (palpebral), followed by cornea, sclera (anterior), conjunctiva (bulbar), sclera (posterior), iris-ciliary body, aqueous humor, and choroid-retinal pigment epithelium in order of decreasing magnitude, indicating that the drug absorbs into the eye. The overall results of the study indicate that the pharmacokinetic parameters derived from the two formulations are similar, suggesting that the formulation changes are not clinically relevant.

Reviewer's Overall Assessment:

The proposed drug product is a locally acting ophthalmic solution and does not show systemic accumulation after topical administration. Several formulations were used during the clinical development. The Applicant provided the batch analysis results comparing the physico-chemical properties of the formulations used in the Phase 2/Phase 3 clinical studies. The slight difference in the osmolality range (240-250 mOsm/kg vs. 290-300 mOsm/kg) is not expected to cause a difference in the drug product's ocular distribution, safety or effectiveness.

In addition, the Applicant provided supportive pharmacokinetic data in the rabbit-animal model indicating that the distribution of the drug in the eye is comparable between the formulations used in the Phase 3 studies. Therefore, the Applicant's request for a waiver of the submission of in vivo bioavailability/ bioequivalence studies supporting the bridging of the formulations used throughout the product's development is **granted**.

From a Biopharmaceutics perspective, the provided information is **acceptable** and NDA 208073 for Xiindra (lifitegrast ophthalmic solution) 5.0% is recommended for **APPROVAL**.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics recommends **APPROVAL** of NDA 208073 for
Xiidra (lifitegrast) Solution, 50 mg/mL.

7/14/15

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Elsbeth Chikhale's Biopharmaceutics assessment and recommendation.

7/14/15

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics, OPQ

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

Applicant's Response: None. Refer to the submission for information provided by the applicant.

Reviewer's Assessment:

See question 29 above

2.3.P.6 Reference Standards or Materials

36. 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: None. Refer to the submission for information provided by the applicant.

Reviewer's Assessment:

See question 29 above

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

37. 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: None.

Reviewer's Assessment:

None of the materials used in the manufacturing of the drug substance or the drug product were of biological origin or derived from biological sources

38. 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: None.

Reviewer's Assessment:

Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Acceptable
Microbiologist/Yuansha Chen, Ph.D.
July 27, 2015

Supervisor Comments and Concurrence:
Quality Assessment Lead (Acting)/John Arigo, Ph.D.
July 27, 2015

39. Is the applicant's claim for categorical exclusion acceptable?

    The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The claim was accompanied by the required statement of no extraordinary circumstances.

40. Is the applicant's Environmental Assessment adequate for approval of the application?

    Not applicable

Applicant's Response: None. Refer to the submission for information provided by the applicant.

Reviewer's Assessment: The categorical exclusion claim is appropriate for the anticipated amount of drug to be used, and the calculation is accurate. The expected introduction concentration (EIC) of (b) (4) ppb is almost an order of magnitude below the 1 ppb categorical exclusion value. In light of new draft environmental assessment (EA) guidance, Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (FDA 2015), FDA conducted a literature search and examined the clinical and nonclinical data submitted with the application for any signals of estrogenic, androgenic, or thyroid activity. No signals were found. The applicant also described quantitative structure–activity relationship (QSAR) modeling that they conducted that showed no molecular substructures or reactive groups in lifitegrast, such as acid chlorides, isocyanates, anhydrides, or α, β-unsaturated carbonyls (e.g., acrylates, acrylamides, and quinones), associated with likely modes of toxic actions. Finally, an adequate statement of no extraordinary circumstances is present.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The claim for a categorical exclusion from an

EA is acceptable.
James P. Laurenson, CDER/OPQ/ONDP EA Team, 7/22/2015

Secondary Review Comments and Concurrence:
Concur.
M. Scott Furness, CDER/OPQ/ONDP

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

Pending

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name:	
Dosage form, route of administration	Dosage: Route:	
Controlled drug substance symbol (if applicable)		
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		

Conclusion:

(b) "Full Prescribing Information" Section

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

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

Conclusion:

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

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

Conclusion:

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

(Attach proposed text)

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

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)		

Conclusion:

2. Labels

1) Immediate Container Label

(Attach the proposed container label here)

Reviewer's Assessment:

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

*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.
**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:

2) Cartons

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))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
"See package insert for dosage information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

Conclusion:

II. List of Deficiencies To Be Communicated

A. Complete Response Comments:

- Regarding your response to the Information Request dated 02-Jun-2015, we still believe that there is no adequate safety information to support the drug substance specification limit of (b)(4) ppm for (b)(4). Since no detectable levels of (b)(4) were present in the late-stage process batches tested to date (detection limit of (b)(4) ppm), we maintain our previous recommendation to reduce the specifications to as low as reasonably possible.
- Since your limit for (b)(4) is not acceptable, we cannot accept the (b)(4) provision for (b)(4) proposed in the drug substance specification. Remove the (b)(4) provision for this impurity.
- The unspecified impurities, (b)(4) each exceed the identification and qualification limits of 10 ppm for leachables. Provide safety data to qualify the leachables at the observed levels. The drug product specification should include a test and suitable acceptance criteria for the above referenced leachables.

B. Other Comments

- In the Amendment dated 16-Jun-2015, you provided the method validation report for *Assay, Purity, Impurities, and Identification Test by HPLC (Test Method TM.2975)*. The (b)(4) does not appear to give (b)(4) (b)(4) (b)(4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. Optimize the method (b)(4) (b)(4) for all potential degradation pathways or develop a new method that is stability-indicating.

- The proposed bulk hold time up to 90 days is acceptable with the assigned shelf life of (b)(4) months provided they meet the finished drug product specification at the end of the shelf life. Note that the assigned shelf life includes the bulk hold time.

- A (b)(4) months shelf life may be assigned for the drug product stored at 25°C/ (b)(4)% RH pending identification and qualification of the 3 unspecified leachables to establish the safety level of these impurities.

- The reconciliation table submitted in your amendment dated 6/10/2015 (table 1 of question 10) is unclear, incomplete, and inaccurate. Consider the following recommendations when you revise the reconciliation table and/or submit any new tables.

    - The table should contain acceptance criteria for actual yield (minimum and maximum of the corresponding theoretical yield) for each phase of production as per CFR211.186(b)(7).

- Provide definitions of the items listed in the first left column of the table, and indicate how they are calculated.
- Waste/loss/rejects during manufacturing should be indicated for each step with proper explanation.
- The actual yield for formulation (b) (4) should be the amount of solution available for filling plus that used for sampling, excluding any waste/loss.
- Provide the actual and theoretical yield for packaging. The actual yield for this step should be (b) (4) .
- The reported (b) (4)

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IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208073	**Submission Type: Priority**	**Established/Proper Name: ?**
Applicant: Shire Development LLC	**Letter Date: 2/25/2015**	**Dosage Form: Ophthalmic Solution**
Chemical Type:	**Stamp Date: 2/25/2015**	**Strength: 5.0%**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	Yes		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			None

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☒	☐	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product	☐	☒	
19.	Other	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned			☒	☐	
21.	End of Phase II/Pre-NDA Agreements			☒	☐	The applicant provided stability data for lots with "atypical matter." It was determined that these lots could be used for supportive stability data, and may be used for re-test and shelf life dating. As per agreement, the applicant provided additional stability data for new drug substance and drug product lots (without atypical matter) to support assignment of a retest date and shelf-life.
22.	SPOTS (Special Products On-line Tracking System)			☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application			☐	☒	
24.	Comparability Protocol(s)[2]			☒	☐	The applicant provided comparability protocol encompassing DS, DP, process, and facility. The protocol is vague and covers almost all possible changes to the NDA.
25.	Other			☐	☒	
Quality Considerations					
26.	Drug Substance Overage			☐	☒	
27.	Design Space	Formulation		☐	☒	
28.		Process		☐	☒	
29.		Analytical Methods		☐	☒	
30.		Other		☐	☒	
31.	Real Time Release Testing (RTRT)			☐	☒	
32.	Parametric Release in lieu of Sterility Testing			☐	☒	
33.	Alternative Microbiological Test Methods			☐	☒	
34.	Process Analytical Technology[1]			☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		☒	☐	
36.		Excipients		☒	☐	
37.		Microbial		☒	☐	
38.	Unique analytical methodology[1]			☐	☒	
39.	Excipients of Human or Animal Origin			☐	☒	
40.	Novel Excipients			☐	☒	
41.	Nanomaterials[1]			☐	☒	
42.	Hold Times Exceeding 30 Days			☐	☒	
43.	Genotoxic Impurities or Structural Alerts			☐	☒	
44.	Continuous Manufacturing			☐	☒	
45.	Other unique manufacturing process[1]			☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).			☐	☒	
47.	New delivery system or dosage form[1]			☐	☒	
48.	Novel BE study designs			☐	☒	
49.	New product design[1]			☐	☒	
50.	Other			☐	☒	

[1]Contact Office of Testing and Research for review team considerations

[2]Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	
	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: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
	DRUG SUBSTANCE INFORMATION				

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	
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? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o 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) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o 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	☒	☐	☐	
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used	☒	☐	☐	Four new drug product batches manufactured with lots of drug substance without the "atypical matter" are on stability with 3 months stability data and plans to submit 6 months before the mid cycle. The 3 original primary batches (drug substance batches with "atypical matter") are with 21 months data.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o 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) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o 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 ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
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?	☒	☐	☐	The drug product formulation used in the first Phase 3 study (OPUS-1, study # 1118-KCS-200) differs from the formulation used in the remaining Phase

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C. FILING CONSIDERATIONS					
	(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)				3 studies (OPUS-2, study 1118-DRY-300; SONATA, study 118-DRY-400; and OPUS-3, study SHP606-304) and the TBM formulation . The difference between these formulations is caused by the removal of (b) (4) from the later Phase 3 and TBM formulation . All formulations meet the same drug product acceptance criteria. In vitro comparability using CMC data to bridge the formulations are provided in section 3.2.P.2.2.1.
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.	☐	☒	☐	Eventhough the drug product is locally acting in the eye, the Applicant has provided plasma pharmacokinetic results for the drug product (section 2.7.2). Section 1.12.15 contains a request for waiver of in vivo bioavailability or bioequivalence studies to support the bridging of formulations. The Applicant cited 21 CFR § 320.22(b)(1).
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☒	☐	☐	
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?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk	☐	☐	☐	

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C. FILING CONSIDERATIONS					
	○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ 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: ○ LAL instead of rabbit pyrogen ○ Mycoplasma 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				

The drug substance is a white to offwhite powder practically insoluble in water. Aqueous solubility at higher pH (>6.0). The applicant identified (b)(4) polymorphic forms and an anhydrous form. Solubility of individual polymorphs and the amorphous forms are not provided. (b)(4) is used as the drug substance. The correlation diagram of polymorphic forms is hard to read.

List of manufacturing and testing sites for the API are provided.

(b)(4)

The synthesis of drug substance (b)(4) and a discussion of possible impurities (along with purging studies) are included.

(b)(4)

the individual impurities were not screened per ICH M7. Other reagents or impurities with known genoxicity were evaluated. A detailed description is provided.

The drug substance specifications has tests for ID, appearance, purity, assay, residual solvents, microbial limits, (b) (4). Most specified impurities are controlled at NMT (b) (4)% or less. (b) (4) is controlled at NMT(b) (4)%. Toxicity study is provided. (b) (4)

The applicant has included controls for (b) (4) as it could be an impurity (b) (4). In-house methods are HPLC, GC, (b) (4). The applicant has provided only a summary for the non-compendial methods. Sample (b) (4) should be requested if polymorphic forms are found to be critical.

Batch data for Phase III clinical, primary stability, development, and validation batches are provided. Data shows low impurity levels.

Container closure: LDPE (b) (4) No dessicant used.

Stability specifications, post approval stability commitment and stability protocol under accelerated (b) (4), intermediate (b) (4), and long term (b) (4) (b) (4) storage conditions provided. There are no obvious trends in the stability data.

Addresses and contact information for the drug product manufacturing and testing sites are provided.

The drug product formulation consists of Lifitegrast drug substance (API), NaCl (b) (4) and pH adjusters. All the excipients are USP/NF grade. No novel excipients or excipients of human/animal origin.

The drug product solution is (b) (4)

Proposed drug product specifications include appearance, color, pH, osmolality, assay, degradants, (b) (4) (b) (4) (b) (4)

non-compendial analytical methods is provided. The applicant identified (b) (4) as a potential degradant, the rest are process impurity for the API. Stability data for the API does not show its formation, however (b) (4) the API may lead to this impurity. The applicant did not identify any degradant due to (b) (4) DP and DS is manufactured/handled (b) (4) . Batch data included in this submission shows low impurity levels.

Lifitegrast Ophthalmic Solution, 5.0% utilizes (b) (4) and an (b) (4) foil (b) (4) pouch as the primary packaging system. The (b) (4) is formed, filled, and sealed (b) (4) conditions. The (b) (4) LDPE with an overflow volume of (b) (4). Target fill is (b) (4) mL solution. A description of the (b) (4) foil (b) (4) is provided.

Stability specifications, post approval stability commitment and stability protocol under accelerated (40°C ± 2°C/75%RH ± 5%RH), intermediate (30°C ± 2°C/65%RH ± 5%RH), and long term (25°C ± 2°C/60%RH ± 5%RH) storage conditions provided. The applicant provided 21 month long term stability data for 3 drug product batches under long term storage conditions. However due to atypical impurities, they submitted 3 M data for three additional batches (see meeting minutes). 6M data points will be submitted prior to the midcycle. No obvious trends in the stability data are noted.

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
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