CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208694Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208694
Review # 2
May 15, 2017

Drug Name/Dosage Form	Cetirizine Ophthalmic Solution, 0.24%
Strength	0.24%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Nicox Ophthalmics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	4/18/2016
Amendment	5/3/2016
Amendment	5/18/2016
Amendment	7/11/2016
Amendment	7/22/2016
Amendment	8/8/2016
Amendment	8/19/2016
Amendment	9/21/2016
Amendment	9/30/2016
Resubmission	3/8/2017

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Drug Substance	Haripada Sarker	ONDP/DNDAPI/NDBI
Drug Product	Yushi Feng	ONDP/DNDP-I/Branch III
	William McCalmont	ONDP/DNDP-I/Branch III
Microbiology	Neal Sweeney	OPF/DMA/MABII
Biopharmaceutics	Banu Zolnik	ONDP/DB/Branch I
Process	Sung Kim	OPF/DPAIII/PABVII
Facility	Frank Wackes	OPF/DIA/IABII
Regulatory Business Process Manager	Erin Andrews	OPRO/DRBPMI/RBPMBI
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP

Laboratory (OTR)	NA	
Environmental Assessment (EA)	Yushi Feng	ONDP/DNDP-I/Branch III

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	5/2/2017	Reviewed by Dr. Haripada Sarker
	Type III			Active	11/14/2012	Found adequate for an ophthalmic solution product by a review dated 14 Nov 2012. Updates since the last review have been reviewed.
	Type III			Active	10/23/2012	Found adequate for an ophthalmic solution product by a review dated 25 Aug 1998. Updates since the last review have been reviewed.
	Type III			Active	08/23/2016	LOA is located in Vol.9.1 This DMF is reviewed.
	Type III			Active	12/11/2013	Found adequate for an ophthalmic solution product by a review dated 5 May 2004.
	Type III			Active	12/18/2012	Found adequate for an ophthalmic solution product by a review dated 10 Aug 2009. Updates since the last review have been

						reviewed.
(b) (4)	Type III		(b) (4)	Active	09/12/2013	Found adequate for an ophthalmic suspension product by a review dated 12 Sep 2013. Updates since the last review have been reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		5/10/2017	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Drug substance, process, quality micro and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1 dated 23-Sep-2016.

As documented in this resubmission Review #2, all drug product issues have been satisfactorily resolved. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 17-Apr-2017.

Therefore, NDA 208694 is recommended for approval from Product Quality perspective.

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

II. Summary of Quality Assessments

A. Product Overview

Proprietary Name of the Drug Product	ZERVIATE
Non Proprietary Name of the Drug Product	Cetirizine ophthalmic solution
Non Proprietary Name of the Drug Substance	Cetirizine hydrochloride
Proposed Indication(s) including Intended Patient Population	For the treatment of ocular itching associated with allergic conjunctivitis.
Duration of Treatment	NA
Maximum Daily Dose	(b) (4) (one drop in each affected eye twice daily).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4). DMF (b) (4) was found adequate by Dr. Sarker on 5/2/2017.

ii. Drug Product Quality Summary

Cetirizine ophthalmic solution, 0.24% is a sterile, buffered, clear, colorless aqueous solution preserved with benzalkonium chloride in a multi-dose ophthalmic low density polyethylene plastic dropper bottles with 2 presentations, a 5 mL fill in a 7.5 mL dropper bottle, or a 7.5 mL fill in a 10 mL dropper bottle, both with an LDPE plastic dropper tip and polypropylene cap.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, BAK, EDTA, particulate appearance, specific gravity, pH, osmolality, minimum fill, APHA color, viscosity, particulate matter, and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 6 registration batches (3 batches for 5 mL fill in 7.5 mL bottle and 3 batches for 7.5 mL fill in 10 mL bottle) of drug products in the commercial container closure system at the commercial scale of (b) (4). All batches complied with the proposed specification.

In the resubmission dated 3/8/2017, stability data updated to eighteen months for three 5 mL fill registration batches and fifteen months for 7.5 mL fill registration batches at long term condition (25°C/40%RH) are provided at the commercial scale. Six month accelerated stability data for both container closure configurations was submitted in the original NDA. There is no trend observed for all the test parameters when the drug products were stored at long term storage condition (25°C/40%RH). These results support both the expiration dating period and storage statement listed below. The applicant withdrew the Comparability Protocol (CP) per the Agency's recommendation on 9/21/2016. Additionally the pharm/tox reviewer Dr. Andrew McDougal has indicated via email on 5/10/2017 that there are no safety concerns on the two leachables (b) (4). Recalculation of impurities, and BAC assay was reviewed and found acceptable in this resubmission.

1. Strength: 0.24%
2. Description/Commercial Image: A clear, colorless aqueous solution.
3. Summary of Product Design: Cetirizine ophthalmic solution.
4. List of Excipients: See Drug Product Section Review, below.
5. Process Selection (Unit Operations Summary)

(b) (4)

(b) (4)

process. In-process controls (IPCs) include (b) (4) Commercial manufacturing process is anticipated to produce the comparable quality as that of registration stability batches considering the same scale of (b) (4) L), manufacturing process, equipment and IPCs as that used for the manufacture of registration batches.

a. Sterilization processes of the drug product, as applicable
The subject drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. The process involves (b) (4) (b) (4)

b. Critical equipment: NA

6. Container Closure: A 7.5 mL or 10 mL white low-density polyethylene (LDPE) bottle, a natural color LDPE dropper tip, and a white polypropylene (PP) (b) (4) closure.
7. Expiration Date & Storage Conditions: 30 months with the storage statement of store at 15°C to 25°C (59°F to 77°F).

iii. Biopharmaceutics Consideration

The proposed drug product is an ophthalmic solution. Therefore, there is no dissolution information for this drug product.

Bridging of the Formulations:
During clinical development, the Applicant evaluated different formulations of cetirizine ophthalmic solution. The approval of the application relies on the four clinical trials (Studies 11-100-0012, 13-100-0002, 12-100-0006, 14-100-0006), and single PK Study (14-100-0007). Although the formulation used in the Phase 3 efficacy and safety studies is listed as AFH-002, the formulation is identical to the to-be-marketed formulation. Therefore there is no need for bridging between the to-be-marketed formulation and formula AFH-002.

Biowaiver:

A biowaiver request is not submitted, nor required because the Applicant conducted a PK study (Study#14-100-0007) following a single drop and twice-daily dosing in healthy subjects. The Office of Clinical Pharmacology will evaluate the PK study.

C. Special Product Quality Labeling Recommendations: None

D. Final Risk Assessment:

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	Formulation includes a preservative; sterilization and (b) (4) manufacturing processes have been validated. DP specification includes sterility testing.	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters	M	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	L	AET performed on routine stability.
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	7.5-mL LDPE bottle with 5 mL fill volume and 10-mL LDPE bottle with 7.5 mL fill volume; drop size study and the minimal weight loss observed support deliverable	L	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Clinically relevant specification; stability studies show no significant change.	L L	

pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Buffered formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>.	L	
Extractables and Leachables	• Container closure	M	The original NDA has provided extractables and leachables data on the clinical batches for 3 month and 6 month at accelerated and long term storage conditions.	M	We except to have the complete extractables and leachables data through the expiry date in the NDA resubmission.

[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.

QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 208694
Review # 1
Sep 23, 2016

Drug Name/Dosage Form	Cetirizine Ophthalmic Solution, 0.24%
Strength	0.24%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Nicox Ophthalmics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	4/18/2016
Amendment	5/3/2016
Amendment	5/18/2016
Amendment	7/11/2016
Amendment	7/22/2016
Amendment	8/8/2016
Amendment	8/19/2016
Amendment	9/21/2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Application Technical Lead	Chunchun Zhang	ONDP/DNDP-I/Branch III
Drug Substance	Haripada Sarker	ONDP/DNDAPI/NDBI
Drug Product	Yushi Feng	ONDP/DNDP-I/Branch III
Microbiology	Neal Sweeney	OPF/DMA/MABII
Biopharmaceutics	Banu Zolnik	ONDP/DB/Branch I
Process	Sung Kim	OPF/DPAIII/PABVII
Facility	Frank Wackes	OPF/DIA/IABII
Regulatory Business Process Manager	Erin Andrews	OPRO/DRBPMI/RBPMBI
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Laboratory (OTR)	NA	
Environmental Assessment (EA)	Yushi Feng	ONDP/DNDP-I/Branch III

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Cetirizine dihydrochloride drug substance	Adequate	9/9/2016	Reviewed by Dr. Haripada Sarker
	Type III		Bottle closure and dropper tip	Active	11/14/2012	Found adequate for an ophthalmic solution product by a review dated 14 Nov 2012. Updates since the last review have been reviewed.
	Type III		Plastic bottles	Active	10/23/2012	Found adequate for an ophthalmic solution product by a review dated 25 Aug 1998. Updates since the last review have been reviewed.
	Type III		Colorant for bottle	Active	08/23/2016	LOA is located in Vol.9.1 This DMF is reviewed.
	Type III		Colorant for closure	Active	12/11/2013	Found adequate for an ophthalmic solution product by a review dated 5 May 2004.
	Type III		Resin for bottle and dropper tip	Active	12/18/2012	Found adequate for an ophthalmic solution product by a review dated 10 Aug 2009. Updates since the last review have been

						reviewed.
(b) (4)	Type III		(b) (4)	Active	09/12/2013	Found adequate for an ophthalmic suspension product by a review dated 12 Sep 2013. Updates since the last review have been reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		8/23/2016	Andrew McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substance, drug product, biopharmaceutics and quality micro aspects.
However, the outcome of the most recent inspection of drug substance manufacturing facility [redacted] (b) (4) has resulted in Office of Process and Facilities recommending Withhold. Therefore, NDA 208694 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 discussion.

Action letter language, related to critical issues such as expiration date:
The following CR statements about the unacceptable manufacturing facility [redacted] (b) (4) [redacted] (b) (4) should be included in the CR letter:

During a recent inspection of the [redacted] (b) (4) *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.*

II. Summary of Quality Assessments

A. Product Overview

Proprietary Name of the Drug Product	ZERVIATE
Non Proprietary Name of the Drug Product	Cetirizine ophthalmic solution
Non Proprietary Name of the Drug Substance	Cetirizine hydrochloride
Proposed Indication(s) including Intended Patient Population	For the treatment of ocular itching associated with allergic conjunctivitis.
Duration of Treatment	NA
Maximum Daily Dose	[redacted] (b) (4) (one drop in each affected eye twice daily).
Alternative Methods of	NA

Administration	

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The applicant cross-referenced the CMC information for the drug substance to DMF [redacted] (b) (4) DMF [redacted] (b) (4) was found adequate by Dr. Sarker on 9/9/2016.

ii. Drug Product Quality Summary

Cetirizine ophthalmic solution, 0.24% is a sterile, buffered, clear, colorless aqueous solution preserved with benzalkonium chloride in a multi-dose ophthalmic low density polyethylene plastic dropper bottles with 2 presentations, a 5 mL fill in a 7.5 mL dropper bottle, or a 7.5 mL fill in a 10 mL dropper bottle, both with an LDPE plastic dropper tip and polypropylene cap.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, BAK, EDTA, particulate appearance, specific gravity, pH, osmolality, minimum fill, APHA color, viscosity, particulate matter, and sterility. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 6 registration batches (3 batches for 5 mL fill in 7.5 mL bottle and 3 batches for 7.5 mL fill in 10 mL bottle) of drug products in the commercial container closure system at the commercial scale of [redacted] (b) (4). All batches complied with the proposed specification.

Twelve months of stability data for three 5 mL fill registration batches and nine months of stability data for 7.5mL fill registration batches at long term condition (25°C/40%RH) are provided at the commercial scale. Six month accelerated stability data for both container closure configurations is submitted in the NDA. There is no trend observed on all the test parameters when the drug products were stored at long term storage condition (25°C/40%RH). These results support both the expiration dating period and storage statement listed below. The applicant withdrew the Comparability Protocol (CP) per the Agency's recommendation on 9/21/2016.

1. Strength: 0.24%
2. Description/Commercial Image: A clear, colorless aqueous solution.
3. Summary of Product Design: Cetirizine ophthalmic solution.
4. List of Excipients: See Drug Product Section Review, below.
5. Process Selection (Unit Operations Summary)

[redacted] (b) (4)

(b) (4)

process. In-process controls (IPCs) include (b) (4) Commercial manufacturing process is anticipated to produce the comparable quality as that of registration stability batches considering the same scale of (b) (4) L), manufacturing process, equipment and IPCs as that used for the manufacture of registration batches.

a. Sterilization processes of the drug product, as applicable
The subject drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. (b) (4) (b) (4) were adequately validated.

b. Critical equipment: NA

6. Container Closure: A 7.5 mL or 10 mL white low-density polyethylene (LDPE) bottle, a natural color LDPE dropper tip, and a white polypropylene (PP) (b) (4).
7. Expiration Date & Storage Conditions: (b) (4) months with the storage statement of store at (b) (4)

iii. Biopharmaceutics Consideration

The proposed drug product is an ophthalmic solution. Therefore, there is no dissolution information for this drug product.

Bridging of the Formulations:
During clinical development, the Applicant evaluated different formulations of cetirizine ophthalmic solution. The approval of the application relies on the four clinical trials (Studies 11-100-0012, 13-100-0002, 12-100-0006, 14-100-0006), and single PK Study (14-100-0007). Although the formulation used in the Phase 3 efficacy and safety studies is listed as AFH-002, the formulation is identical to the to-be-marketed formulation. Therefore there is no need for bridging between the to-be-marketed formulation and formula AFH-002.

Biowaiver:
A biowaiver request is not submitted, nor required because the Applicant conducted a PK study (Study#14-100-0007) following a single drop and twice-daily dosing in healthy subjects. The Office of Clinical Pharmacology will evaluate the PK study.

C. Special Product Quality Labeling Recommendations: None

D. Final Risk Assessment:

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	Formulation includes a preservative; sterilization and (b) (4) manufacturing processes have been validated. DP specification includes sterility testing.	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters	M	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	L	AET performed on routine stability.
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	7.5-cc LDPE bottle with 5 mL fill volume and 10-cc LDPE bottle with 7.5 mL fill volume; drop size study and the minimal weight loss observed support deliverable	L	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Clinically relevant specification; stability studies show no significant change.	L L	

pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Buffered formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>.	L	
Extractables and Leachables	• Container closure	M	The original NDA has provided extractables and leachables data on the clinical batches for 3 month and 6 month at accelerated and long term storage conditions.	M	We except to have the complete extractables and leachables data through the expiry date in the NDA resubmission.

[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.

BIOPHARMACEUTICS

Product Background:

NDA 208694

Drug Product Name / Strength: Cetirizine Ophthalmic Solution, 0.24%

Route of Administration: Topical, ocular

Applicant Name: Nicox Ophthalmics, Inc.

List Submissions being reviewed:
Seq.0001 dated 04/18/2016
Seq. 005 dated 5/23/2016

Review:
The proposed drug product is an ophthalmic solution. Therefore, there is no dissolution information for this drug product.

Bridging of the Formulations:

During the clinical development, the Applicant evaluated different formulations of cetirizine ophthalmic solution. At the beginning of the development, the Applicant conducted three clinical trials (b) (4) (b) (4) (b) (4)

The approval of the application relies on the four clinical trials (Studies 11-100-0012, 13-100-0002, 12-100-0006, 14-100-0006), and single PK Study (14-100-0007). Table 1 shows the composition information for each formulation used in the pivotal and supportive clinical studies. Although, the formulation used in the Phase 3 efficacy and safety studies is listed as AFH-002, the formulation is identical to the to-be-marketed formulation. Therefore there is no need for bridging between the to-be-marketed formulation and formula AFH-002. There are differences in the composition of the formulations used in the Studies 11-100-0004 and 11-100-0013; however, since these formulations are used in supportive clinical trials, bridging of these formulations is not needed.

Table 1: Composition information for the formulations used in the pivotal and supportive clinical trials

Component	Function	To-Be-Marketed Formulation	Formula AFH-002	AC- 170	Formulation
		Concentration (mg/mL)	Concentration (mg/mL)	Concentration (mg/mL)	Concentration (mg/mL)
Cetirizine (b) (4)		2 85 (2 40 as (b)	2 85 (2 40 as cetirizine (b)		(b) (4)
Benzalkonium chloride					(b) (4)
Glycerin					
Sodium phosphate, dibasic (b) (4)					
Edetate disodium (b) (4)					
Polyethylene glycol 400					
Polysorbate 80					
Hypromellose					
(b) Sodium hydroxide	pH adjustment				(b) (4)
		PK study and safety study	Phase 3 efficacy and safety study	Safety and comfort	Efficacy and safety
		Study 14-100-0007 Study 14-100-0006	Study 11-100-0012 Study 13-100-0002 Study 12-100-0006	Study 11-100-0013	Study 11-100-0004
		Pivotal Studies		Supportive Studies	

Biowaiver:

A biowaiver request is not submitted, nor required because the Applicant conducted a PK study (Study#14-100-0007) following a single drop and twice-daily dosing in healthy subjects. The Office of Clinical Pharmacology will evaluate the PK study.

CONCLUSION AND RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 208694 for Cetirizine Ophthalmic Solution, 0.24% is recommended for **Approval.**

Primary Biopharmaceutics Reviewer Name and Date:

8/19/2016
Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with Dr. Sizanli Zolnik's assessment and recommendation.
8/23/2016
Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Elsbeth Chikhale

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Banu Zolnik

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

MICROBIOLOGY

Product Background:

NDA: 208694

Drug Product Name / Strength: Zerviate (Cetirizine Ophthalmic Solution, 0.24%)

Route of Administration: Topical ocular

Applicant Name: Nicox Ophthalmics, Inc., 777 Main Street, Suite 1292, Fort Worth, TX 76102

Manufacturing Site:
(Drug Product)
Akorn, Inc. (Drug Product)
72-6 Veronica Ave
Somerset, NJ 08873

(b) (4)

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
18 April 2016	18 April 2016	N/A	03 May 2016
08 Aug 2016	08 Aug 2016	N/A	N/A
21Sept 2016	21Sept 2016		

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: (None).

S Drug Substance

Drug substance is supplied as non-sterile, and the drug substance specification does not include microbial limits testing. Drug substance loss on drying acceptance criterion is (b) (4)%.

All excipients (except WFI described below) are tested for microbial limits according to USP <61> with the following acceptance criteria:

Table 1: Microbiological Quality of Excipients

Excipient	Microbial Limits Acceptance Criteria
Benzalkonium chloride, (b) (4) (b) (4)	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g
Glycerin	TAMC: NMT CFU/g TYMC: NMT CFU/g
Sodium phosphate, dibasic, (b) (4)	TAMC: NMT CFU/g TYMC: NMT CFU/g
Edetate disodium, (b) (4)	TAMC: NMT (b) (4) FU/g TYMC: NMT FU/g
Polyethylene glycol 400	TAMC: NMT CFU/g TYMC: NMT CFU/g
Polysorbate 80	TAMC: NMT CFU/g TYMC: NMT CFU/g
Hypromellose	TAMC: NMT CFU/g TYMC: NMT CFU/g
Sodium hydroxide	TAMC: NMT (b) (4) CFU/g TYMC: NMT FU/g
Hydrochloric acid	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g

Table 1 was reproduced in part from applicant's Table 3.2.P.4.1-1, located in 3.2.P.4.1, specifications.pdf, page 1.

Reviewer's Assessment: Microbiological quality acceptance criteria for excipients comply with those specified by USP <1111> for non-sterile substances/excipients for pharmaceutical use. Drug substance specifications do not include microbial limits testing. However, there is adequate in-process (b) (4) control (b) (4) (b) (4) the drug product formulation was shown to be antimicrobial.

ADEQUATE

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a multi-dose ophthalmic solution having a pH of approximately 7 and osmolarity of 300 mOsmol/kg, so as to be biocompatible with the ocular surface. The drug product is filled in 7.5 cc (5 mL fill) and 10 cc (7.5 mL fill) LDPE dropper bottles with LDPE plastic dropper tips and polypropylene caps.
- Drug product composition – The drug product solution contains the following components: cetirizine dihydrochloride (2.4 mg/mL), benzalkonium chloride

(0.10 mg/mL), glycerin [redacted] (b) (4) sodium phosphate, dibasic, [redacted] (b) (4) edetate disodium, [redacted] (b) (4) polyethylene glycol 400 [redacted] (b) (4) polysorbate 80 [redacted] (b) (4) and hypromellose [redacted] (b) (4)

- Description of container closure systems – All container closure components are manufactured by [redacted] (b) (4)

  5 mL product configuration: 7.5 cc [redacted] (b) (4) LDPE bottle, [redacted] (b) (4) LDPE dropper tip

  7.5 mL product configuration: 10 cc [redacted] (b) (4), 10 cc Bottle: [redacted] (b) (4) LDPE dropper tip

Reviewer's Assessment:

The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the drug product topical ophthalmic route of administration.

ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Container/closure integrity was validated for both the 5 mL and 7.5 mL product container/closure configurations via dye ingress testing, and reported in Akorn test reports 42-906 and 42-744, respectively. For each product configuration four sets of ten (40 total) drug product units were randomly selected for testing. The first set of ten samples was completely submerged in a container covering the test units with the methylene blue solution (0.075%), and a vacuum of 10" Hg was applied for a 30-minute period. A second set of ten units was similarly submerged in dye without the vacuum (static conditions). The third set of ten units was inoculated with 1 µL of 0.075% methylene blue to demonstrate detection of 1 µL ingress. The fourth set of ten units was intentionally breached (by making two holes near the neck of the bottle using a 27G needle). All samples were evaluated for the presence of dye using UV-VIS spectrophotometer at 664nm. Results are summarized below:

Table 2: Drug Product Container/Closure Integrity (Dye Ingress) Results

Test Group	Absorbance (664 nm) Range for 10 samples	
	5 mL configuration	7.5 mL configuration

Vacuum Challenge	-0.0027 – 0.0033	-0.0010 – 0.0007
Static Challenge	-0.0047 – 0.0010	-0.0013 – 0.0010
1 µL-Inoculated (+) Control	0.0700 – 0.0868	0.0401 – 0.0553
Breached Control	3.6343 – 3.8663	4.0716 – 4.2757

Results demonstrated that challenged (vacuum and static conditions) units met the acceptance criteria by exhibiting UV-absorbance values substantially below the (b) (4) µg/mL) detection limit for the dye. The detection limit was demonstrated measuring the absorbance of a dilution series of the dye.

Reviewer's Assessment: Demonstration of drug product container-closure integrity was consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) ICH Q8(R2) Pharmaceutical Development.

ADEQUATE

Antimicrobial Effectiveness Testing

Drug product batches formulated with 0%, 25%, 50%, 75%, and 100% of labeled benzalkonium chloride (BAC) concentration were tested using USP <51> Antimicrobial Effectiveness Testing. Method suitability was demonstrated using product diluted (1:10 for *A. brasiliensis*, *C. albicans*, *S. aureus*, *P. aeruginosa*, and *E. coli*, and 1:100 for *S. aureus*) in Saline (0.9%) Test Solution with Polysorbate 80 (0.05%), and required recovery from product to be within 2-fold of the recovery observed from control. Antimicrobial effectiveness testing results, presented in Akorn Report 20-12, demonstrated that product formulated with 25, 50, 75, and 100% BAC met USP <51> category 1 acceptance criteria. Additionally, the unpreserved was shown to pass AET for the *A. brasiliensis*, *C. albicans*, *S. aureus*, and *E. coli*, challenge organisms, but failed the *P. aeruginosa* challenge portion of the test. Drug product release and stability specifications include preservative content acceptance criterion of (b) (4)% to (b) (4)% for BAC.

AET stability results, stated as meeting USP <51> category 1 acceptance criteria, were provided for the following product configurations with the corresponding drug substance and container/closure suppliers:

Table 3: Submitted AET Stability Data for Drug Product Configurations

DP Configuration	DS Supplier	C/C Supplier	Long Term (25°C/40%RH) AET Stability

			Results Provided
5 mL/7.5 cc	(b) (4)		12 months*
7.5 mL/10 cc			6 months*
(b) (4)			36 months
5 mL/7.5 cc			24 months
(b) (4)			6 months

* Ongoing long term stability includes AET testing at 12, 24, and 36 months.

Whereas a (b) (4) acceptable 24- and 36-month AET results were provided. Drug product commercial production will utilize the (b) (4) drug substance supplier and (b) (4) container/closure system.

Reviewer's Assessment: Demonstration of drug product antimicrobial effectiveness was consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) ICH Q8(R2) Pharmaceutical Development, and (3) Q1A(R2) Stability Testing of New Drug Substances and Products.

ADEQUATE

P.3 Manufacture

P.3.1 Manufacturers

(Drug Product)
Akorn, Inc. (Drug Product)
72-6 Veronica Ave
Somerset, NJ 08873

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4) **Manufacturing Process**

Building and facilities

The drug product will be manufactured at the Akorn facility located at 72 Veronica Street, Somerset, NJ. (b) (4)

(b) (4)

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(b) (4)

Reviewer's Assessment:

ADEQUATE

Reviewer's Assessment of Sterilization Process Validation Information (Section P.3.5 Process Validation and/or Evaluation): Sterilization and (b) (4) validation/requalification studies and results were consistent with those delineated in the FDA Guidances for Industry (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Sterile Drug Products Produced by (b) (4) — Current Good Manufacturing Practice, as well as common industry practice.

ADEQUATE

P.5 Control of Drug Product

P. 5.1 Specification

P.5.2 Analytical Procedures

- Endotoxin – Not required for topical ophthalmic products.
- Sterility – Drug product specifications include USP <71> Sterility Testing.

Reviewer's Assessment:

ADEQUATE

P.5.3 Validation of Analytical Procedures

Endotoxins

Reviewer's Assessment:
N/A (Not required for topical ophthalmic products.)

Sterility

Sterility test method suitability testing consisted of triplicate studies that demonstrated that when the final rinse was inoculated (<100 CFU) with either *P. aeruginosa, B. subtilis, C. albicans, S. aureus, A. brasiliensis*, or *C. sporogenes*, no recovery inhibition could be detected.

Reviewer's Assessment: The drug product specification (sterility testing) and sterility test method validation/suitability complies with USP <71> Sterility Test, and FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

ADEQUATE

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment:

(See Section P.1 of this review.)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The applicant proposes a (b) (4) month storage at (b) (4) C. The primary stability program contains multiple drug product stability batches to account for two different drug substance suppliers and two different container suppliers, as well the two proposed container/fill sizes. For primary stability batches Sterility and Antimicrobial Effectiveness testing (AET) is performed at 0, 3, 6, 12, 15, 24, and 36 months for long term storage conditions (25°C ± 2°C; 40% ± 5% RH), and at 0, and 6 months for accelerated storage conditions 40°C ± 2°C; NMT 25% RH).

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

- Sterility / Container Closure Integrity – The applicant commits to complete the ongoing primary stability studies for drug product batches on long term stability, and also commits to place one batch of each bottle size on stability per year on the long term stability program. Sterility testing will be performed at the 0, 12, 24, and 36 month stability test stations. AET is not included in the post-approval stability protocol.

- Endotoxin – Endotoxin testing is not included in the stability protocol, and is not required for topical ophthalmic products.

P.8.3 Stability Data

Available data for the primary stability batches showed that sterility and AET acceptance criteria were met. See Section P.2.5. Preservative Effectiveness for a summary of drug product AET stability test results.

Reviewer's Assessment: The submitted stability protocol, commitment and data comply with Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

ADEQUATE

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: There are no excipients of human or animal origin used in the manufacture of CetirizineOphthalmic Solution, 0.24%.

R Regional Information

Executed Batch Records

Reviewer's Assessment: Two representative executed batch records were provided for review: PD15-015 (7.5 mL fill in 10 cc bottles) and PD15-005 (5 mL fill in 7.5 cc bottles).

Comparability Protocols

(b) (4)

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(b) (4)

[redacted]

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

2.A. Package Insert

Reviewer's Assessment: Drug product labeling specifies that the drug product is applied topically to each eye. The drug product is not diluted prior to use. Therefore, no dilution/storage/microbiological challenge studies are necessary.

Post-Approval Commitments:

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies: (None)

Primary Microbiology Reviewer Name and Date:

Neal J. Sweeney, Ph.D. September 21, 2016

Quality Assessment Lead (Acting)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Bryan S. Riley, Ph.D. September 21, 2016

Branch Chief (Acting)

OPQ/OPF/DMA/Branch II

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Bryan Riley

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Neal Sweeney

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MICROBIOLOGY

Product Background:

NDA: 208694

Drug Product Name / Strength: Zerviate (Cetirizine Ophthalmic Solution, 0.24%)

Route of Administration: Topical ocular

Applicant Name: Nicox Ophthalmics, Inc., 777 Main Street, Suite 1292, Fort Worth, TX 76102

Manufacturing Site:
(Drug Product)
Akorn, Inc. (Drug Product)
72-6 Veronica Ave
Somerset, NJ 08873

(b) (4)

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
18 April 2016	18 April 2016	N/A	03 May 2016
08 Aug 2016	08 Aug 2016	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: Incomplete sterility assurance component of Comparability Protocol for manufacturing the (b) (4) at a proposed alternate manufacturing site.

S Drug Substance

Drug substance is supplied as non-sterile, and the drug substance specification does not include microbial limits testing. Drug substance loss on drying acceptance criterion is (b) (4) %.

All excipients (except WFI described below) are tested for microbial limits according to USP <61> with the following acceptance criteria:

Table 1: Microbiological Quality of Excipients

Excipient	Microbial Limits Acceptance Criteria
Benzalkonium chloride, (b) (4) (b) (4)	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g
Glycerin	TAMC: NMT CFU/g TYMC: NMT CFU/g
Sodium phosphate, dibasic, (b) (4)	TAMC: NMT (b) (4) CFU/g TYMC: NMT FU/g
Edetate disodium, (b) (4)	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g
Polyethylene glycol 400	TAMC: NMT (b) (4) CFU/g TYMC: NMT CFU/g
Polysorbate 80	TAMC: NMT CFU/g TYMC: NMT CFU/g
Hypromellose	TAMC: NMT CFU/g TYMC: NMT CFU/g
Sodium hydroxide	TAMC: NMT (b) (4) CFU/g TYMC: NMT FU/g
Hydrochloric acid	TAMC: NMT CFU/g TYMC: NMT FU/g

Table 1 was reproduced in part from applicant's Table 3.2.P.4.1-1, located in 3.2.P.4.1, specifications.pdf, page 1.

Reviewer's Assessment: Microbiological quality acceptance criteria for excipients comply with those specified by USP <1111> for non-sterile substances/excipients for pharmaceutical use. Drug substance specifications do not include microbial limits testing. However, there is adequate in-process (b) (4) control (b) (4) and the drug product formulation was shown to be antimicrobial. **ADEQUATE**

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a multi-dose ophthalmic solution having a pH of approximately 7 and osmolarity of 300 mOsmol/kg, so as to be biocompatible with the ocular surface. The drug product is filled

in 7.5 cc (5 mL fill) and 10 cc (7.5 mL fill) LDPE dropper bottles with LDPE plastic dropper tips and polypropylene caps.

- Drug product composition – The drug product solution contains the following components: cetirizine dihydrochloride (2.4 mg/mL), benzalkonium chloride (0.10 mg/mL), glycerin ([redacted] (b) (4) sodium phosphate, dibasic, [redacted] (b) (4) edetate disodium, [redacted] (b) (4) polyethylene glycol [redacted] (b) (4) polysorbate 80 [redacted] (b) (4) and hypromellose [redacted] (b) (4)
- Description of container closure systems – All container closure components are manufactured by [redacted] (b) (4)

  5 mL product configuration: 7.5 cc [redacted] (b) (4) LDPE bottle, [redacted] (b) (4) LDPE dropper tip

  7.5 mL product configuration: 10 cc [redacted] (b) (4) LDPE bottle, 10 cc Bottle: [redacted] (b) (4) LDPE dropper tip

Reviewer's Assessment:

The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the drug product topical ophthalmic route of administration.

ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Container/closure integrity was validated for both the 5 mL and 7.5 mL product container/closure configurations via dye ingress testing, and reported in Akorn test reports 42-906 and 42-744, respectively. For each product configuration four sets of ten (40 total) drug product units were randomly selected for testing. The first set of ten samples was completely submerged in a container covering the test units with the methylene blue solution (0.075%), and a vacuum of 10" Hg was applied for a 30-minute period. A second set of ten units was similarly submerged in dye without the vacuum (static conditions). The third set of ten units was inoculated with 1 µL of 0.075% methylene blue to demonstrate detection of 1 µL ingress. The fourth set of ten units was intentionally breached (by making two holes near the neck of the bottle using a 27G needle). All samples were evaluated for the presence of dye using UV-VIS spectrophotometer at 664nm. Results are summarized below:

Table 2: Drug Product Container/Closure Integrity (Dye Ingress) Results

Test Group	Absorbance (664 nm) Range for 10 samples	
	5 mL configuration	7.5 mL configuration
Vacuum Challenge	-0.0027 – 0.0033	-0.0010 – 0.0007
Static Challenge	-0.0047 – 0.0010	-0.0013 – 0.0010
1 µL-Inoculated (+) Control	0.0700 – 0.0868	0.0401 – 0.0553
Breached Control	3.6343 – 3.8663	4.0716 – 4.2757

Results demonstrated that challenged (vacuum and static conditions) units met the acceptance criteria by exhibiting UV-absorbance values substantially below the [redacted] (b) (4) µg/mL) detection limit for the dye. The detection limit was demonstrated measuring the absorbance of a dilution series of the dye.

Reviewer's Assessment: Demonstration of drug product container-closure integrity was consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) ICH Q8(R2) Pharmaceutical Development.

ADEQUATE

Antimicrobial Effectiveness Testing

Drug product batches formulated with 0%, 25%, 50%, 75%, and 100% of labeled benzalkonium chloride (BAC) concentration were tested using USP <51> Antimicrobial Effectiveness Testing. Method suitability was demonstrated using product diluted (1:10 for *A. brasiliensis*, *C. albicans*, *S. aureus*, *P. aeruginosa*, and *E. coli*, and 1:100 for *S. aureus*) in Saline (0.9%) Test Solution with Polysorbate 80 (0.05%), and required recovery from product to be within 2-fold of the recovery observed from control. Antimicrobial effectiveness testing results, presented in Akorn Report 20-12, demonstrated that product formulated with 25, 50, 75, and 100% BAC met USP <51> category 1 acceptance criteria. Additionally, the unpreserved was shown to pass AET for the *A. brasiliensis*, *C. albicans*, *S. aureus*, and *E. coli*, challenge organisms, but failed the *P. aeruginosa* challenge portion of the test. Drug product release and stability specifications include preservative content acceptance criterion of (b) (4)% to (b) (4)% for BAC.

AET stability results, stated as meeting USP <51> category 1 acceptance criteria, were provided for the following product configurations with the corresponding drug substance and container/closure suppliers:

Table 3: Submitted AET Stability Data for Drug Product Configurations

DP Configuration	DS Supplier	C/C Supplier	Long Term (25°C/40%RH) AET Stability Results Provided
5 mL/7.5 cc	(b) (4)		12 months*
7.5 mL/10 cc			6 months*
(b) (4)			36 months
5 mL/7.5 cc			24 months
(b) (4)			6 months

* Ongoing long term stability includes AET testing at 12, 24, and 36 months.

Whereas a (b) (4) month drug product expiry has been proposed, acceptable 24- and 36-month AET results were provided. Drug product commercial production will utilize the (b) (4) drug substance supplier and (b) (4) container/closure system.

Reviewer's Assessment: Demonstration of drug product antimicrobial effectiveness was consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) ICH Q8(R2) Pharmaceutical Development, and (3) Q1A(R2) Stability Testing of New Drug Substances and Products.

ADEQUATE

P.3 Manufacture

P.3.1 Manufacturers

(Drug Product)
Akorn, Inc. (Drug Product)
72-6 Veronica Ave
Somerset, NJ 08873

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4) **Manufacturing Process**

Building and facilities

The drug product will be manufactured at the Akorn facility located at 72 Veronica Street, Somerset, NJ. (b) (4)

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:

ADEQUATE

Reviewer's Assessment of Sterilization Process Validation Information (Section P.3.5 Process Validation and/or Evaluation): Sterilization and [redacted] (b) (4) **validation/requalification studies and results were consistent with those delineated in the FDA Guidances for Industry (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Sterile Drug Products Produced by** [redacted] (b) (4) **— Current Good Manufacturing Practice, as well as common industry practice.**

ADEQUATE

P.5 Control of Drug Product

P. 5.1 Specification

P.5.2 Analytical Procedures

- Endotoxin – Not required for topical ophthalmic products.
- Sterility – Drug product specifications include USP <71> Sterility Testing.

Reviewer's Assessment:

ADEQUATE

P.5.3 Validation of Analytical Procedures

Endotoxins

Reviewer's Assessment:
N/A (Not required for topical ophthalmic products.)

Sterility

Sterility test method suitability testing consisted of triplicate studies that demonstrated that when the final rinse was inoculated (<100 CFU) with either *P. aeruginosa, B. subtilis, C. albicans, S. aureus, A. brasiliensis*, or *C. sporogenes*, no recovery inhibition could be detected.

Reviewer's Assessment: The drug product specification (sterility testing) and sterility test method validation/suitability complies with USP <71> Sterility Test, and FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

ADEQUATE

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment:

(See Section P.1 of this review.)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The applicant proposes a (b) (4) month storage at (b) (4) C. The primary stability program contains multiple drug product stability batches to account for two different drug substance suppliers and two different container suppliers, as well the two proposed container/fill sizes. For primary stability batches Sterility and Antimicrobial Effectiveness testing (AET) is performed at 0, 3, 6, 12, 15, 24, and 36 months for long term storage conditions (25°C ± 2°C; 40% ± 5% RH), and at 0, and 6 months for accelerated storage conditions 40°C ± 2°C; NMT 25% RH).

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

- Sterility / Container Closure Integrity – The applicant commits to complete the ongoing primary stability studies for drug product batches on long term stability, and also commits to place one batch of each bottle size on stability per year on the long term stability program. Sterility testing will be performed at the 0, 12, 24, and 36 month stability test stations. AET is not included in the post-approval stability protocol.

- Endotoxin – Endotoxin testing is not included in the stability protocol, and is not required for topical ophthalmic products.

P.8.3 Stability Data

Available data for the primary stability batches showed that sterility and AET acceptance criteria were met. See Section P.2.5. Preservative Effectiveness for a summary of drug product AET stability test results.

Reviewer's Assessment: The submitted stability protocol, commitment and data comply with Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

ADEQUATE

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: There are no excipients of human or animal origin used in the manufacture of CetirizineOphthalmic Solution, 0.24%.

R Regional Information

Executed Batch Records

Reviewer's Assessment: Two representative executed batch records were provided for review: PD15-015 (7.5 mL fill in 10 cc bottles) and PD15-005 (5 mL fill in 7.5 cc bottles).

Comparability Protocols

(b) (4)

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(b) (4)

[redacted]

INADEQUATE

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

2.A. Package Insert

Reviewer's Assessment: Drug product labeling specifies that the drug product is applied topically to each eye. The drug product is not diluted prior to use. Therefore, no dilution/storage/microbiological challenge studies are necessary.

Post-Approval Commitments:

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies:

(b) (4)

Primary Microbiology Reviewer Name and Date:

Neal J. Sweeney, Ph.D. August 24, 2016

Quality Assessment Lead (Acting)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Bryan S. Riley, Ph.D. August 24, 2016

Branch Chief (Acting)

OPQ/OPF/DMA/Branch II

Bryan Riley

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Neal Sweeney

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