CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Approval

Satisfactory information and responses have been submitted to support product quality (drug substance, drug product, quality microbiology, and manufacturing process).

All the facilities are acceptable based on the profile. An overall acceptable cGMP recommendation for all the facilities was issued on 2/4/2020.

Therefore, NDA 212520 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

Oxymetazoline Hydrochloride Ophthalmic Solution, 0.1% is a clear, colorless to slightly yellow, preservative-free, sterile solution filled into clear, (b) (4) single dose vials. Each mL of the drug product contains 1 mg of oxymetazoline HCl, equivalent to (b) (4) of oxymetazoline free base.

Proposed Indication(s) including Intended Patient Population	For the treatment of acquired blepharoptosis (droopy eyelid) in adults.
Duration of Treatment	One drop topically in each eye once daily
Maximum Daily Dose	0.07 mg (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance Oxymetazoline Hydrochloride to DMF [redacted]. DMF [redacted] was found adequate by Dr. Sharon Kelly.

Drug Product: Adequate

Oxymetazoline Hydrochloride Ophthalmic Solution, 0.1% is a clear, colorless to slightly yellow, preservative-free, sterile solution filled into clear, [redacted] single dose vial which is individually wrapped in a protected foil pouch. The individual foil-pouched vials are further packaged into a child-resistant zipper bag that is placed into a carton.

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, pH, osmolality, identity, assay, impurities, viscosity, particulate matter, weight loss, dye ingress immersion test, sterility, and control of potentia [redacted]. The specification is acceptable. All analytical methods are described in reasonable detail and have been adequately validated.

Stability data is updated to 15 months for one registration batch and 12 months for two other registration batches at long term storage 25°C/40% RH, 12 months at 30°C/65% RH for and 6 months 40°C/25% RH for with horizontally orientation for three batches. Three registration batches are manufactured at the commercial scale of [redacted] Kg at the commercial drug product manufacturing site. A slight increasing trend was observed for impurity [redacted] when the drug products were stored at long term storage condition (25°C). The extractable study indicated low risk and therefore no leachable study is needed. Elemental impurity risk assessment was performed on 3 drug product batches and the levels for class 1, 2A, B and 3 elemental impurities were below 30% of ICH Q3D option 1 established limits. These results support both the expiration dating period of 24 months and storage statement listed below.

The storage statement is: "Store at 20°C-25°C (68°F-77° [redacted] Protect from excessive heat. Keep out of reach of children."

Labeling: Adequate

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

Manufacturing: Adequate

(b) (4)

All the facilities are acceptable based on the profile and no PAI is scheduled. Therefore, the overall recommendation of "Approval" was entered for the NDA into Panorama by OPMA on 2/4/2020.

Biopharmaceutics: Adequate

No biopharmaceutics review is needed as the proposed drug product is an ophthalmic solution.

Microbiology (if applicable): Adequate

The (b) (4) and sterility assurance is found acceptable.

C. Risk Assessment

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Eval.	Lifecycle Considerations
Sterility	Formulation Container closure Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure[1] Raw materials	L		L	
Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L		L	

Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M	(b) (4)	L	
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure Process parameters Scale/equipment	M		L	

D. List of Deficiencies for Complete Response: NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D., 6/12/2020

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Treatment of acquired blepharoptosis
NDA Number	212520
Assessment Cycle Number	MR01
Drug Product Name/Strength	Oxymetazoline Hydrochloride Ophthalmic Solution, 0.1%
Route of Administration	Topical, ocular
Applicant Name	RevitaLid, Inc., a wholly-owned subsidiary of Osmotica Pharmaceutical Corp.
Therapeutic Classification/ OND Division	Ophthalmic
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
eCTD seq #0001	09/16/2019
eCTD seq #0006	10/23/2019
eCTD seq #0010	02/06/2020
eCTD seq #0013	02/26/2020

List Submissions being assessed (table): 09/16/2019, 10/23/2019, 02/06/2020, 02/26/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks:

- **An Information Request was sent to the applicant on 10/08/2019 and a response was received on 10/23/2019.**
- **An Information Request was sent to the applicant on 01/07/2020 and a response was received on 02/06/2020.**
- **An Information Request was sent to the applicant on 02/24/2020 and a response was received on 02/26/2020. The original deficiency are italicized below.**

Concise Description of Outstanding Issues

(List bullet points with key information and update as needed): None

Supporting Documents:

- **Microbiology reviews 076749s17.doc (inadequate), dated 9/9/2015, and 076749S17a1.doc (adequate), dated 9/23/2015**

S DRUG SUBSTANCE-N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product-** A clear, colorless to slightly yellow, aseptically prepared, preservative-free, sterile solution, pH of 5.8-6.8, osmolality of (b) (4) mOsmol/kg, containing 0.035 mg/drop of API, supplied as a (b) (4) target fill volume in a 0.5 ml (b) (4) vial, and given topically.

- **Drug product composition-**

Ingredient	Quantity (mg/drop)	Function
Oxymetazoline hydrochloride, USP	0.035	API
Sodium chloride, USP	(b) (4)	(b) (4)
Potassium chloride, USP		
Calcium chloride, (b) (4) USP		
Magnesium chloride, (b) (4), USP		
Sodium acetate, (b) (4) USP		
Sodium citrate (b) (4) NF		
Hypromellose, USP (b) (4)		
Water for injection		
Hydrochloric acid, NF	q.s.	pH adjusting agent
(b) (4) NF	(b) (4)	

- **Description of container closure system-** A unit dose, (b) (4) individually wrapped in a foil pouch. (b) (4) .

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

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(eCTD seq #0001: Section 3.2.P.5.3, MP-249-SR Verification Report for Limit of Methylene Blue Dye (for MTM-6380), MP-270-SR Validation of Dye Ingress Immersion Testing (for MTM-6380); eCTD seq #0006: Section 3.2.P.7, MP-149-SR Microbial Ingress Summary Report; Section 3.2.P.5.2, MTM-SC-MB-6380 v8.0 Dye Ingress Immersion)

Note to reviewer: The applicant provided results of CCIT by both dye ingress and microbial ingress methods. Since they will be conducting dye ingress along with sterility testing for post-approval stability batches, both CCIT methods will be reviewed.

10/08/2019 Information Request:
You indicate on page 47/152 of the Pharmaceutical Development.pdf that you performed integrity validation for the primary container closure system (CCS) using a microbial ingress test. However, more information is needed for review. Provide the following information:

a. A detailed description of the test procedure and acceptance criteria;
b. Description of any positive and negative controls and how they were prepared. An intentionally breached positive control is recommended;
c. Number of units tested including positive and negative controls, and the actual test results.

10/23/2019 Applicant's response:
The applicant provided the following microbial ingress CCIT information.

Report and protocol-

- Mold Qualification via Microbial Ingress of (b) (4) for Oxymetazoline with (b) (4) located on (b) (4) document number MP-149-SR, approved 10/10/2019
- Mold Qualification via Microbial Ingress of (b) (4) for Oxymetazoline with (b) (4) located on (b) (4) document number MP-149, approved 03/12/2018

450 (b) (4)) from (b) (4) M82603 were tested for CCIT. Five positive and five negative controls were also tested for each (b) (4). Positive controls were breached with a 30G½ needles. Test units and positive controls were submerged in a suspension containing ≥1 x 10^6 CFU/ml of *B. diminuta* and exposed to a vacuum of NLT 5" Hg for NLT 10 minutes. After 10 minutes, the vacuum was released, and the ampoules were then kept in the suspension for 2 hours. The ampoules were then removed and incubated at 30-35 °C for 7 days. Growth promotion controls were inoculated with <100 CFU of the challenge organism.

Acceptance criteria:

- All testing was performed, completed, and documented in accordance with protocol instructions

- All challenged vials were negative for ingress of the microbial suspension- no turbidity
- Pre- and post-vacuum exposure inoculation verifications of the suspension broth had microorganism counts ≥1 x 106 CFU/ml
- Deviations pertaining to this validation must be documented, investigated, and appropriately resolved and addressed in the final report

Results: The acceptance criteria were met. No growth was observed in the test units and negative controls, while growth was observed in deliberately-breached positive controls and growth promotion controls.

The applicant stated that an error in the MTM-SC-MB-6380 v7.0 Dye Ingress Immersion.pdf in eCTD sequence #0001, Section 3.2.P.5.2 was identified. The test method contained an incorrect unit of measure in Section 6.2.1, which was a typographical error. 1 mg was corrected to 1 g in the v8.0 pdf. In addition, some clarification and minor edits were made to the method, which are described in Section 8.0 Revision Summary. The revised MTM-SC-MB-6380 v8.0 Dye Ingress Immersion.pdf was provided in Section 3.2.P.5.2 of this amendment.

CCIT by the dye ingress method

Protocols and reports-

- Dye Ingress Immersion Test, document #MTM-SC-MB-6380, version 8.0, approved 10/8/2019
- Method Validation Summary Report for the Qualification of Dye Ingress Immersion Testing with Methylene Blue Dye, USP using UV-Vis Spectroscopy for use with Oxymetazoline HCl Ophthalmic Solution, 0.1% (b) (4) ml Fill, document #MP-270-SR, approved 07/16/2019
- Method Validation Protocol for the Qualification of Dye Ingress Immersion Testing with Methylene Blue Dye, USP using UV-Vis Spectroscopy for use with Oxymetazoline HCl Ophthalmic Solution, 0.1% (b) (4) ml Fill, document #MP-270, approved 06/28/2019
- Method Verification Summary Report for the Limit of Methylene Blue Dye USP, using UV-Vis Spectroscopy, document #MP-249-SR, approved 05/15/2019
- Method Verification Protocol for the Limit of Methylene Blue Dye USP, using UV-Vis Spectroscopy, document #MP-249, approved 05/07/2019

The (b) (4) vials used for validation were the same as used to package the drug product.

Acceptance criteria:

- The initial 40 containers should contain visible evidence of blue dye ingress. Any units that do not show ingress should be examined to determine the cause

- The results for the second set of 80 containers are acceptable if the spectrophotometer can detect the theoretical 0.5 ppm concentration within the 40 compromised containers, the 40 intact units do not show any dye ingress, and the 5 ppm concentration dye solution and the positive and negative controls meet specifications per MTM-SC-MB-6380. Record the results of the UV-Vis spectrophotometer scans on form FRM-SC-MB-6380-A, Dye Ingress Testing

40 (b) (4) vials with (b) (4) ml fill volumes were weighed in triplicate (average weight: 2.07 g). The vials were prepared by piercing each vial with a 30½ gauge needle, leaving the needle in place, and submerging the vials in a dye bath with a concentration of (b) (4) ppm. The vials were submerged in dye under a vacuum of at least 22" of Hg for NLT 1 hour. The vacuum was then released, and the vials rested for 30 minutes. The vials were reweighed in triplicate, and the average was calculated to be 2.82 g. This average was used to calculate the total dye ingress through the difference in vial weight prior to and after ingress. The average volume of dye ingress was calculated to be 0.75 ml [volume ingress = average weight difference x (1 ml/H_2O density at 22 °C (0.998 g/ml)]. All vials showed dye ingress. The concentration of dye required to ingress into the vial in order to achieve a concentration of 0.5 ppm within the vial was determined to be 0.7 ppm [new bath ppm = LOD x (original container volume + ingress volume)/ingress volume].

A new dye bath was prepared with a concentration of 0.7 ppm. 40 additional vials were prepared with defects and 40 vials had no defects. Two positive controls were prepared by piercing each vial with a 30½ gauge needle, leaving the needle in place, and submerging the vials in the dye bath. Two negative controls were not subjected to immersion in the dye bath. The vials were then placed in a vacuum chamber with a vacuum of at least 22" of Hg for NLT 1 hour. The vacuum was then released, and the vials rested for 30 minutes. The vials and positive and negative controls were examined by a UV-vis spectrophotometer. All vials with a defect confirmed dye ingress by visual examination and showed absorbance at 665. All vials without a defect confirmed no dye ingress by visual examination and showed no absorbance at 665.

Note to reviewer: It is unclear how the 40 additional vials with defects were different from the positive controls; therefore, clarification will be requested.

The acceptance criteria were met for the dye ingress immersion test.

Sensitivity:
Methylene blue conc: (b) (4) % w/v or (b) (4) ppm
The limit of detection is determined to be (b) (4) µg/ml dye ((b) (4) ppm)

(b) (4) vial with (b) (4) ml fill volume
(b) (4)

Minimum detectable ingress volume:

(b) (4)

01/07/2020 Information Request:
Regarding container closure integrity testing by dye ingress immersion for post-approval stability batches, clarify the difference between the "40 additional units with defects" referenced on page 9/45 of the document MP-270-SR Validation of Dye Ingress Immersion Testing (for MTM-6380).pdf and the "positive controls" referenced on the same page.

02/06/2020 Applicant's response:
40 vials were prepared with defects by piercing the vial with a 30 ½ gauge needle. These vials were the positive controls used in the first step of the procedure to determine the appropriate concentration of the dye bath. They were weighed before and after being exposed to the vacuum and dye bath to determine the ingress volume. 40 additional positive control units with defects were prepared the same way for the next step of the procedure, which was testing performed with the calculated dye bath concentration. These positive control vials went through the entire procedure, including submerging the vials in the dye bath and scanning the vials on the UV-Vis, to validate that the method was appropriate.

Assessment: *Adequate*

The applicant has adequately validated the integrity of the proposed commercial container closure system.

Antimicrobial Effectiveness Testing

N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Assessment: N/A

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(b) (4)

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