CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213581Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213581
Assessment # 1

Drug Product Name	Atropine Sulfate
Dosage Form	Ophthalmic solution
Strength	1%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Paragon BioTeck Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	May 26, 2021	All disciplines
Quality Amendment	Aug 4, 2021	Drug product
Quality Amendment	Nov 24, 2021	Drug substance, drug product, quality microbiology, manufacturing process
Quality Amendment	Feb 3, 2022	Quality microbiology
Quality Amendment	Feb 14, 2022	Manufacturing process
Quality Amendment	Feb 15, 2022	Drug product
Quality Amendment	Feb 24, 2022	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jing Li	Suong Tran
Drug Product	Anne Marie Russell	Chunchun Zhang
Manufacturing	Upasana Sahu	Vidya Pai
Microbiology	Karthik Krishnan	Christine Craig
Biopharmaceutics	Parnali Chatterjee	Om Anand
Regulatory Business Process Manager	Kelly Ballard	

Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Anne Marie Russell	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	1/13/2022	LoA dated 8/21/2020; Reviewed by Jing Li
	III			Adequate	NA	LoA dated 9/26/2020
	III			Adequate	NA	LoA dated 3/9/2021

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	139379	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	7/16/2021	Dr. Erin Ruhland
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 213581, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Atropine Sulfate ophthalmic solution USP, 1%. All information requests and review issues have been addressed.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on Feb 23, 2022.

The drug product is regulated as a dug device combination product per the Genus decision. The 356h form was updated to indicate this classification on 2/14/2022. CDRH confirmed that no CDRH GMP/QS consults is necessary for this product.

Therefore, NDA 213581 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

Atropine Sulfate Ophthalmic Solution USP, 1% is a sterile, preservative-free, aqueous solution and packaged in 1 mL LDPE (b) (4) *single dose vials with 0.4 mL fill volume. One strip of 5 single dose containers is packaged into a foil pouch.*

Proposed Indication(s) including Intended Patient Population	For the treatment of cycloplegia, mydriasis and the penalization of the healthy eye in the treatment of amblyopia
Duration of Treatment	One drop topically to the eye; twice daily
Maximum Daily Dose	(b) (4) mg/day (see the package insert for details)

Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Atropine sulfate is a synthetic small molecule and a colorless crystal or a white crystalline powder. The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) which was found adequate by Dr. Jing Li on 1/13/2022.

Drug Product: Adequate

Atropine Sulfate Ophthalmic Solution USP, 1% is a sterile, preservative-free, single dose ophthalmic solution. All the excipients are compendial including boric acid, hydroxypropyl methylcellulose (HPMC), hydrochloric acid/sodium hydroxide, and water for injection.

The revised drug product specifications are acceptable and meet the USP monograph. The following quality attributes are included: description, ID, pH, osmolality, assay, impurities, particulate matter, minimum fill volume, viscosity, content uniformity, and sterility. The proposed limit for any unspecified impurity NMT 1.0% was found acceptable by P/T reviewer Dr. Erin Ruhland on 7/16/2021. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in ICH Q3D guidance. We note there is a risk of (b) (4)

The applicant submitted the risk assessment per the agency's request. Dr. Dan Berger from the OPQ (b) (4) working group confirmed the risk of (b) (4) (b) (4)

The commercial container closure for the proposed product is a 1.0 mL low-density polyethylene (LDPE) (b) (4) single dose one-piece vial. Each vial is filled with a target quantity of 0.4 mL. A 5-vial card is packaged in a pre-printed, non-sterile foil pouch. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted 18 months stability data at long term (25°C/40%RH) and 6 months at accelerated condition (40°C/25%RH) for the three registration batches (lots # 910085, 910086 and 910087) in (b) (4) vials in foil pouch. All the quality attributes met the specifications and no

obvious trend was observed. The product is stable during the freeze-thaw and photostability studies. Therefore, no cautious statement is proposed in the labeling. Additionally, the applicant performed in-use stability study to support the proposed 30-days in use period when the product is stored in the (b) (4) vials without foil pouches. Therefore, the expiration date of 24 months is granted when stored at 20 °C- 25 °C.

The storage statement is "Store at 20°C-25°C (68°F-77°F)." and will be finalized at the OND's labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The manufacturing process for Atropine Sulfate Ophthalmic Solution USP, 1% is (b) (4). All the facilities associated with the application appear acceptable to support the manufacturing of the proposed drug product based on the facilities history and recent inspection findings for the drug product manufacturing site Unither (FEI: 1314625).

Biopharmaceutics: Adequate

21CFR 320.22 (e) good cause waiver to support the waiver of BA/BE studies for the proposed drug product.

Microbiology (if applicable): Adequate

The manufacturing process includes (b) (4) and (b) (4). This application is recommended for approval on the basis of product quality microbiology.

C. Risk Assessment

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

Sterility	Formulation Container closure Process parameters Scale/equipment Site	H		L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure Raw materials	L	(b) (4)	L	
Uniformity of Dosage unit	Formulation Container closure Process parameters Scale/equipment	M		L	
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure Process parameters Scale/equipment	M		L	
(b) (4) impurity risk assessment	Formulation Excipients	H		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Feb 24, 2022

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CHAPTER VII: BIOPHARMACEUTICS MEMO

NDA: 213581
Drug Product Name / Strength: Atropine Sulfate Ophthalmic Solution, USP, 1%
Route of Administration: Ophthalmic Solution
Applicant Name: Paragon BioTeck, Inc.
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Poonam Delvadia, Ph.D., Om Anand, Ph.D.

Background:
NDA 213581-ORIG-1 was submitted on 05/26/2021 to seek approval for Atropine Sulfate Ophthalmic Solution, USP, 1% to induce mydriasis (pupil dilation), cycloplegia, and for the treatment of amblyopia by penalization of healthy eye (b) (4) *via* the 505 (b)(2) regulatory pathway. According to the Applicant, dosing of the proposed product is age-dependent. The proposed dosing for patients 3 months and above is one (1) drop to be instilled topically to cul-de-sac of conjunctiva, forty (40) minutes prior to intended dilation time. For patients three (3) years and above, doses may be repeated up to twice daily, as needed.

The current NDA is relying upon safety, efficacy, and pharmacokinetic data for Atropine Sulfate Ophthalmic Solution, USP, 1% from published literature[1, 2].

REVIEW SUMMARY:
The proposed product is a sterile, preservative-free, aqueous solution containing 1% w/v atropine sulfate that is (b) (4) in a 0.4 mL single-use, low density polyethylene (LDPE) vial for topical ocular application.

The proposed product is a currently marketed, unapproved product composed of boric acid (b) (4) Hypromellose (b) (4), hydrochloric acid and sodium hydroxide (pH adjuster), and water for injection along with 1%w/v atropine sulfate (which is similar to the LDs). However, the LDs are multi-dose vials that contain benzalkonium chloride as a preservative; whereas the proposed drug product will be available as a single-use vial and therefore is preservative-free (without benzalkonium chloride). Apart from the presence of benzalkonium chloride in the LDs, the proposed product is in same dosage form, for similar route of administration, and for similar indication as the LDs. Comparative compositional similarity for the proposed drug product with the LDs under NDAs, 206289 and 208151 is provided in **Table 1**.

Based on internal discussions with the Clinical Team, the waiver of bioavailability studies for the proposed drug product should be under 21 CFR 320.22 (e), 'Good Cause' as the waiver is compatible with protection of public health.

The assessment of 'Good Cause Waiver' for Atropine Sulfate Ophthalmic Solution, USP, 1% is reviewed by Office of Clinical Pharmacology (OCP).

RECOMMENDATION: From the Biopharmaceutics perspective, NDA 213581-ORIG-1 for Atropine Sulfate Ophthalmic Solution, USP, 1% is **adequate**.

Table 1. Comparative compositional similarity between the previously approved Listed Drugs under NDAs, 206289 and 208151 and currently proposed formulation under NDA 213581

Ingredient	NDA 206289 Akorn	NDA 208151 Alcon	(b) (4)	NDA 213581 Paragon
Atropine Sulfate	USP	USP		USP
Benzalkonium Chloride	NF	NF		-
Dibasic Sodium Phosphate	USP	-		-
Edetate Disodium	USP	-		-
Hypromellose	USP	USP		USP
Monobasic Sodium Phosphate	USP	-		-
Boric Acid	-	NF		NF
Sodium Hydroxide	NF	NF		NF
Hydrochloric Acid	NF	NF		NF
Water for Injection	USP	USP		USP

Table 2. Comparative pharmacokinetics of atropine following ocular administration of Atropine Sulfate Ophthalmic Solution, USP, 1% from published literature[1, 2]

Study	Dosing	Subjects	PK Parameter measured for l-hyoscyamine				
			C_{max} (pg/mL)	t_{max} (min)	AUC (h*ng/mL)	$t_{½}$ (h)	F%
Kaila, 1999	Single IV dose	6 (1M/5F) 24-29 years	N/A	N/A	Mean 1.79±0.64 Range 1.15 - 3	Mean 2.97±1.22 Range 1.3-4.3	N/A
	Topical ocular – 0.3 mg		Mean 288±73 Range 166 – 355	Mean 28±27 Range 3-60	Mean 1.02±0.33 Range 0.35-1.25	Mean 2.45±0.76 Range 1.5-3.6	Mean 63.5±28.6 Range 19-95
Lahdes 1988	Topical ocular – 0.4 mg	8 (7M/1F) 56-66 years	Mean 860±402	N/A	Mean 0.73±0.4 Range 0.04-1.29	N/A	N/A

[1] Kaila, T, Korte J-M, Saari KM (1999) Systemic bioavailability of ocularly applied 1% atropine eyedrops. *Acta Ophthalmol. Scad.* 77: 193-196.

[2] Lahdes K, Kaila T, Huupponen R, Salminen L, Lisalo E (1988) Systemic absorption of topically applied ocular atropine. *Clin. Pharmacol. Ther.* 44(3):310-314.

Parnali Chatterjee

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213581
Assessment Cycle Number	01
Drug Product Name/ Strength	Atropine Sulfate / 1%
Route of Administration	Topical Ocular
Applicant Name	Paragon BioTeck Inc.
Therapeutic Classification/ OND Division	CDER/OND/OSM/DO
Manufacturing Site	Unither Manufacturing, LLC. 331 Clay Road, Rochester NY 14623 FEI: 1314625
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq #0001	05/26/2021
eCTD seq #0007	11/24/2021
E-mail correspondence	01/17/2022

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

Remarks: Atropine Sulfate Ophthalmic Solution USP, 1% is indicated for the treatment of cycloplegia, mydriasis and the penalization of the healthy eye in the treatment of amblyopia. The proposed drug product is a sterile, preservative-free, aqueous solution and packaged in 1 mL LDPE (b) (4) single dose vials with 0.4 mL fill volume. One strip of 5 single dose containers is packaged into a foil pouch. This review includes information requests sent on 10/13/2021 and responses received on 11/24/2021.

Concise Description of Outstanding Issues: None identified.

Supporting Documents: None.

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, pgs. 1-2/4 in "description-and-composition.pdf"

Atropine Sulfate Ophthalmic Solution USP, 1% is a sterile, preservative-free, aqueous solution manufactured by (b) (4) (b) (4) and (b) (4) 5 vials (0.4 mL per unit-dose vial) and packaged into a non-sterile foil pouch.

Drug product composition

Ingredient	Quantity per mL	Function
Atropine Sulfate, USP-NF	10 mg	Active Ingredient
Boric Acid, USP-NF	(b) (4)	
Hydroxypropyl Methylcellulose, USP-NF (HPMC, (b) (4)		
Hydrochloric Acid (b) (4)%, USP-NF (b) (4)	As needed	pH adjustment
Sodium Hydroxide, USP-NF (b) (4)	As needed	pH adjustment
Water for Injection, USP-NF (b) (4)	(b) (4)	

Description of container closure system

Section 3.2.P.7, pgs. 2-6/12 in "container-closure-system.pdf"

(b) (4) (primary): (b) (4) 1 mL unit dose vials (b) (4) (b) (4)

Foil Pouch (secondary): Pre-printed, non-sterile foil pouch (b) (4) (b) (4)

Assessment: *Adequate*

The firm provided an adequate description of the drug product's composition and container closure system.

(b) (4)

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