CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208151Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208151
Addendum # 1 to Review # 1
Nov 10, 2016

Drug Name/Dosage Form	Atropine Sulfate Ophthalmic Solution
Strength	1%
Route of Administration	Topically into eye(s)
Rx/OTC Dispensed	Rx
Applicant	Alcon
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	2/12/2016	Product Quality
Amendment to IR	5/5/2016	Product Quality
Amendment to IR	5/12/2016	Product Quality
Amendment to IR	7/12/2016	Product Quality
Amendment to IR	9/14/2016	Product Quality
Amendment to IR	9/16/2016	Product Quality
Amendment to IR	10/7/2016	Product Quality

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/DNDAPI/NDBI
Drug Product	Milton Sloan	ONDP/DNDPI/NDPBIII
Process	Maotang Zhou	OPF/DPAIII/PABVII
Microbiology	Denise Miller	OPF/DMA/MABII
Facility	Vidya Pai	OPF/DIA/IABIII
Biopharmaceutics	Om Anand	ONDP/DB/BBI
Regulatory Business Process Manager	Erin Andrews	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDPI/NDPBIII
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis (EA)	Milton Sloan	ONDP/DNDPI/NDPBIII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate		LoA: 2/10/2015 DMF was found adequate by Dr. David Skanchy on 11/10/2016.
	Type III			Adequate	8/23/2016 by Yushi Feng	LoA: 5/11/2009
	Type III			Adequate	8/23/2016 by Yushi Feng	LoA: 1/31/2013
	Type V			NA		LoA: 8/4/2011
	Type V			NA		LoA: 3/15/2011

[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)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	115869	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Biopharmaceutics, manufacturing process and quality micro reviewers have recommended approval of the NDA as documented in Review #1.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities.

As documented in this Addendum, the IR responses to the referenced drug substance DMF (b) (4) was found adequate as documented in the review dated 11/10/2016 (Please see DMF review in DARRTS). Drug product Review #1 recommended Approval and this addendum upholds the approval recommendation after reviewing the IR responses received on 10/7/2016.

Therefore, NDA 208151 is recommended for approval from the 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

Proposed Indication(s) including Intended Patient Population	An anti-muscarinic agent indicated for Mydriasis; Cycloplegia; Amblyopia (b) (4).
Duration of Treatment	NA
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The applicant cross-referenced the drug substance CMC information to DMF (b) (4) which was found adequate (Reviewed by Dr. David Skanchy, dated 11/10/2016).

ii. Drug Product Quality Summary

ISOPTO® ATROPINE (Atropine Sulfate Ophthalmic Solution) 1% is a sterile, clear, colorless to (b) (4) ophthalmic solution preserved with benzalkonium chloride in a multi-dose low density polyethylene round bottles with 2 presentations, 5 mL fill in a 8 mL round bottle, and 15 mL fill in a 15 mL round bottle, both with an LDPE (b) (4) and red polypropylene (PP) closure.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. There is no overage of the active in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, BAK, pH, osmolality, viscosity, particulate matter, and sterility. The proposed specification is acceptable. All analytical methods are either USP or modified USP methods and are described in reasonable detail and adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved. The ISOPTO® ATROPINE (Atropine Sulfate Ophthalmic Solution) 1% drug product meets the requirements of the USP monograph.

The proposed commercial scale is (b) (4) kg. Batch analyses are provided for 6 registration batches (3 batches for 5 mL fill in 8 mL bottle and 3 batches for 15 mL fill in 15 mL bottle) of drug products in the commercial container closure system at the scales of (b) (4) kg. All batches complied with the proposed specification.

Twenty four months of stability data for six registration batches at long term condition (25°C/40%RH) and 5°C are provided. Six months of accelerated stability data for both container closure configurations is submitted in the NDA.

There are no trends observed on all the test parameters when the drug products were stored at long term storage condition (2-25°C). These results support both the expiration dating period and storage statement listed below.

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

Manufacturing process (b) (4) The drug product container and (b) (4) are pre-sterilized by (b) (4) while the PP closures are also pre-sterilized by (b) (4) Since the applicant has been using the same process for the manufacture of the proposed drug product on commercial scales for over 30 years, this is considered as a mature and low-risk process from a process reviewer's perspective.

a. Sterilization processes of the drug product, as applicable

The drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. The process involves sterile (b) (4).

b. Critical equipment: NA

6. Container Closure: An 8 mL or 15 mL (b) (4) low-density polyethylene (LDPE) round bottle, (b) (4), and a red polypropylene (PP) closure.
7. Expiration Date & Storage Conditions: 24 months with the storage statement of store at 2-25°C (36-77°F).

iii. Biopharmaceutics Consideration

The proposed drug product, Isotpo® Atropine 1.0%, is an ophthalmic solution containing 1.0 % w/v atropine sulfate as the active drug substance. The application is relying on the published literature for pharmacokinetics (PK), safety and efficacy of the proposed drug product.

The applicant requested a waiver of the requirement to provide evidence of in vivo bioavailability (BA) or bioequivalence (BE) under 21 CFR 320.22(e) which states that the FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence. The applicant submitted literature publication containing bioavailability data and the bridge between the formulation used in the publications with the PK information and the proposed drug product is adequate. The PK data will be reviewed by the Office of Clinical Pharmacology (OCP). Even though the applicant submitted a biowaiver request under 21 CFR 320.22(e), the CFR 320.21 requirement for submission of bioavailability and/or bioequivalence data has been met by the provided literature information and therefore a biowaiver request is not needed.

From the Biopharmaceutics perspective there is an adequate bridge between some of the formulations used in the articles submitted to support PK, safety and efficacy and the proposed drug product.

From the Biopharmaceutics perspective, NDA 208151 for Isotpo® Atropine (atropine sulfate ophthalmic solution) 1.0%, is recommended for APPROVAL.

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 (b) (4)	• 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 stability at 24 month.
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	8mL LDPE bottle with 5 mL fill volume and 15 LDPE bottle with 15 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	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	(b) (4) 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	
Weight Change	• Temperature excursions	M	Full 24-month shelf life data is within specification.	L	Significant changes can affect trends in assay, BAC, and osmolality.

[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.

OVERALL ASSESSMENT AND SIGNATURE:

NDA 208151 is recommended for approval from the Product Quality perspective.

Chunchun Zhang, Ph.D.; Acting CMC-Lead and ATL for NDA 208151

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DIVISION OF TRANSPLANT AND OPHTHALMOLOGY DRUG PRODUCTS
OFFICE OF NEW DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

ADDENDUM TO NDA #208151, DRUG PRODUCT REVIEW #1

DATE: Nov. 07, 2016

SUBJECT: Acceptance of IR Amendment Responses and Final Drug Product approval recommendation for NDA 208-151, ISOPTO® Atropine (atropine sulfate ophthalmic solution) 1%

Comment 1 (Sep 29-30, 2016)
Please list hypromellose as an inactive ingredient (b) (4) in labeling (carton, immediate container label, and package insert).

Response for 1 (Oct. 7, 2016):
Alcon agrees and will update the labeling and list hypromellose as inactive ingredient.

Comment 2 (Sep 29-30, 2016)
In your response to Information Request dated 31 August 2016, you made reference to NDAs using the same red colorant, but continued to list as "(b) (4)" polypropylene closure in the text of the amendment, although in the updated Summary of Stability tables you describe as "red". Please clarify, and provide a statement that colorant in closure is the same as referenced.

Response for 2 (Oct. 7, 2016):
As stated in packaging Section 3.2.P.7, the closure is red. We apologize for the incorrect reference to "(b) (4)" polypropylene closure in the paragraph text of Section 3.2.P.8.1, and we have confirmed that the "red" closures lots identified in Tables 3.2.P.8.1-1 and 3.2.P.8.1-2 are indeed "red" closures. A corrected Section 3.2.P.8.1 is provided.

Response Evaluation and Recommendation
The responses for comments 1 and 2 are acceptable. Approval of this application is recommended from the Drug Product perspective. There are no outstanding issues or labeling comments. The sponsor has agreed to accept the proposed labeling revisions. The changes are to be incorporated in the combined final printed label. Please see Drug Product Review #1 for full review details.

Milton J. Sloan, Ph. D., Sr. Chemist, Branch III, Division I, Office of New Drug Product, Office of Product Quality

Balajee Shanmugan, Ph.D., Acting Branch Chief, Branch III, Division I, Office of New Drug Product, Office of Product Quality

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 11/08/2016 05:39 37PM
GUID: 50758d5000003c1b1962e036ea11002c

Milton Sloan

Digitally signed by Milton Sloan
Date: 11/08/2016 04:24 32PM
GUID: 508da72000029fa0e17abc24c6841f0a

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 11/10/2016 02:20 37PM
GUID: 51269608000064178e75377202fe6c5d

QUALITY ASSESSMENT

Recommendation: Pending Recommendation

NDA 208151
Review # 1
Oct 12, 2016

Drug Name/Dosage Form	Atropine Sulfate Ophthalmic Solution
Strength	1%
Route of Administration	Topically into eye(s)
Rx/OTC Dispensed	Rx
Applicant	Alcon
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	2/12/2016	Product Quality
Amendment to IR	5/5/2016	Product Quality
Amendment to IR	5/12/2016	Product Quality
Amendment to IR	7/12/2016	Product Quality
Amendment to IR	9/14/2016	Product Quality
Amendment to IR	9/16/2016	Product Quality

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
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Drug Product	Milton Sloan	ONDP/DNDPI/NDPBIII
Process	Maotang Zhou	OPF/DPAIII/PABVII
Microbiology	Denise Miller	OPF/DMA/MABII
Facility	Vidya Pai	OPF/DIA/IABIII
Biopharmaceutics	Om Anand	ONDP/DB/BBI
Regulatory Business Process Manager	Erin Andrews	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDPI/NDPBIII
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis (EA)	Milton Sloan	ONDP/DNDPI/NDPBIII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Pending		LoA: 2/10/2015 DMF has outstanding IRs to be resolved and therefore is "Deficient" at this time.
	Type III			Adequate	8/23/2016 by Yushi Feng	LoA: 5/11/2009
	Type III			Adequate	8/23/2016 by Yushi Feng	LoA: 1/31/2013
	Type V			NA		LoA: 8/4/2011
	Type V			NA		LoA: 3/15/2011

[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)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	115869	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
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 product, biopharmaceutics, manufacturing process and quality micro aspects. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities.

However, the referenced DMF has outstanding IRs to be resolved and therefore a final assessment of drug substance is pending at this time. Once the responses are evaluated and assessments become available, a final recommendation from OPQ will be documented in an addendum.

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

Proposed Indication(s) including Intended Patient Population	An anti-muscarinic agent indicated for Mydriasis; Cycloplegia; Amblyopia (b) (4).
Duration of Treatment	NA
Maximum Daily Dose	(b) (4)
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) has outstanding IRs to be resolved and therefore is "Deficient" at this time.

ii. Drug Product Quality Summary

ISOPTO® ATROPINE (Atropine Sulfate Ophthalmic Solution) 1% is a sterile, clear, colorless to (b) (4) ophthalmic solution preserved with benzalkonium chloride in a multi-dose low density polyethylene round bottles with 2 presentations, 5 mL fill in a 8 mL

round bottle, and 15 mL fill in a 15 mL round bottle, both with an LDPE (b) (4) and red polypropylene (PP) closure.
All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. There is no overage of the active in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, BAK, pH, osmolality, viscosity, particulate matter, and sterility. The proposed specification is acceptable. All analytical methods are either USP or modified USP methods and are described in reasonable detail and adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved. The ISOPTO® ATROPINE (Atropine Sulfate Ophthalmic Solution) 1% drug product meets the requirements of the USP monograph.
The proposed commercial scale is (b) (4) kg. Batch analyses are provided for 6 registration batches (3 batches for 5 mL fill in 8 mL bottle and 3 batches for 15 mL fill in 15 mL bottle) of drug products in the commercial container closure system at the scales of (b) (4) kg. All batches complied with the proposed specification.
Twenty four months of stability data for six registration batches at long term condition (25°C/40%RH) and 5°C are provided. Six months of accelerated stability data for both container closure configurations is submitted in the NDA.
There are no trends observed on all the test parameters when the drug products were stored at long term storage condition (2-25°C). These results support both the expiration dating period and storage statement listed below.

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

Manufacturing process consists (b) (4) The drug product container and (b) (4) are pre-sterilized by (b) (4) while the PP closures are also pre-sterilized by (b) (4). Since the applicant has been using the same process for the manufacture of the proposed drug product on commercial scales for over 30 years, this is considered as a mature and low-risk process from a process reviewer's perspective.

a. Sterilization processes of the drug product, as applicable

The drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. The process involves sterile (b) (4).

b. Critical equipment: NA

6. Container Closure: An 8 mL or 15 mL (b) (4) low-density polyethylene (LDPE) round bottle, (b) (4), and a red polypropylene (PP) closure.
7. Expiration Date & Storage Conditions: 24 months with the storage statement of store at 2-25°C (36-77°F).

iii. Biopharmaceutics Consideration

The proposed drug product, Isotpo® Atropine 1.0%, is an ophthalmic solution containing 1.0 % w/v atropine sulfate as the active drug substance. The application is relying on the published literature for pharmacokinetics (PK), safety and efficacy of the proposed drug product.

The applicant requested a waiver of the requirement to provide evidence of in vivo bioavailability (BA) or bioequivalence (BE) under 21 CFR 320.22(e) which states that the FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence. The applicant submitted literature publication containing bioavailability data and the bridge between the formulation used in the publications with the PK information and the proposed drug product is adequate. The PK data will be reviewed by the Office of Clinical Pharmacology (OCP). Even though the applicant submitted a biowaiver request under 21 CFR 320.22(e), the CFR 320.21 requirement for submission of bioavailability and/or bioequivalence data has been met by the provided literature information and therefore a biowaiver request is not needed.

From the Biopharmaceutics perspective there is an adequate bridge between some of the formulations used in the articles submitted to support PK, safety and efficacy and the proposed drug product.

From the Biopharmaceutics perspective, NDA 208151 for Isotpo® Atropine (atropine sulfate ophthalmic solution) 1.0%, is recommended for APPROVAL.

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 (b) (4)	• 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 stability at 24 month.
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	8mL LDPE bottle with 5 mL fill volume and 15 LDPE bottle with 15 mL fill volume; drop size study and the minimal weight loss observed support deliverable volume.	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	(b) (4) 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	
Weight Change	• Temperature excursions	M	Full 24-month shelf life data is within specification.	L	Significant changes can affect trends in assay, BAC, and osmolality.

[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.

OVERALL ASSESSMENT AND SIGNATURE:

A final recommendation from drug substance is pending at this time as the referenced DMF has outstanding IRs to be resolved. When the assessment is available, an overall recommendation from OPQ will be documented in an Addendum.

Chunchun Zhang, Ph.D.; Acting CMC-Lead and ATL for NDA 208151

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Reviewer's Assessment: N/A

CHAPTER IV: Labeling

{For NDA only}

R Regional Information

1.14 Labeling

(a) "Highlights" Section (21CFR 201.57(a))
(Attach proposed text)

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Yes	
Dosage form, route of administration	Yes	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	No	Recommend revising see conclusion

Reviewer's Assessment: Pending

Recommend:

ISOPTO® Atropine (atropine sulfate ophthalmic solution, 1%)

1% sterile ophthalmic solution

(b) "Full Prescribing Information" Section
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

(b) (4) ophthalmic solution containing: 1 (b) (4) % (10 mg/mL) atropine sulfate equivalent to 8.3 mg/mL of atropine.

Supplied in 5 mL and 15 mL in plastic DROP-TAINER® dispensers.

Reviewer's Assessment: Pending

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Yes	Ophthalmic solution
Strengths: in metric system	Yes	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	N/A	Revision recommended; Only dosage form and strength information should be included

Recommend:

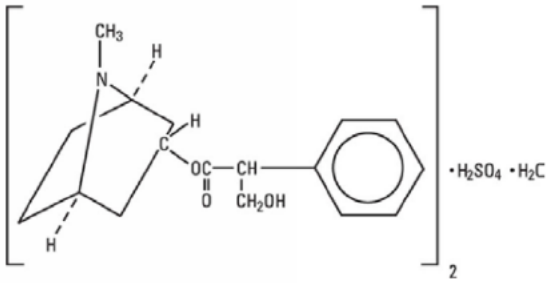
3 DOSAGE FORMS AND STRENGTHS

Ophthalmic Solution: Each mL of ISOPTO® Atropine (atropine sulfate ophthalmic solution, 1%) contains 10 mg/mL of atropine sulfate equivalent to 8.3 mg of atropine.

#11: Description (21CFR 201.57(c)(12))
(Attach proposed text)

11 DESCRIPTION

ISOPTO® Atropine [redacted] a sterile topical ophthalmic solution. Each mL of ISOPTO® Atropine [redacted] contains 10 mg of atropine sulfate. Atropine sulphate is designated chemically as benzeneacetic acid, α-(hydrohymethyl)-,8-methyl-8-aza-bicyclo-[3.2.1]oct-3-yl ester, *endo*-(±)-, sulfate(2:1) (salt), monohydrate. Its [redacted] formula is $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ and it is represented by the chemical structure:



Atropine sulfate is colorless crystals, or white, crystalline powder and has a molecular weight of 694.83.

ISOPTO® Atropine [redacted] has a pH of 3.5 to 6.0.

[redacted] **Active:** atropine [redacted] 1 % (10mg/mL). atropine sulfate equivalent to 8.3 mg/mL of atropine. **Preservative:** benzalkonium chloride 0.01%. [redacted] **Inactives:** boric acid, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

Reviewer's Assessment: Pending

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Yes	Acceptable
Dosage form and route of administration	Yes	Acceptable
Active moiety expression of strength with equivalence statement for salt (if	Yes	Revisions provided

applicable)		
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	No	Revised statement added

Recommend:

11 DESCRIPTION

ISOPTO® Atropine is a sterile topical ophthalmic solution. Each mL of ISOPTO® Atropine contains 10 mg of atropine sulfate equivalent to 8.3 mg of atropine. Atropine sulfate is designated chemically as benzene acetic acid, α-(hydrohymethyl)-,8-methyl-8-aza-bicyclo-[3.2.1]oct-3-yl ester, *endo*-(+)-, sulfate(2:1) (salt), monohydrate. Its (b) (4) formula is $(C_{17}H_{23}NO_3)_2 \bullet H_2SO_4 \bullet H_2O$ and it is represented by the chemical structure:

Structure same as provided in PI

Atropine sulfate monohydrate is colorless crystals or white crystalline powder and has a molecular weight of 694.83. ISOPTO® Atropine 1% contains of 10 mg/mL of atropine sulfate monohydrate equivalent to 9.7 mg/mL of atropine sulfate or 8.3 mg (b) (4) of atropine.

ISOPTO® Atropine has a pH of 3.5 to 6.0.

Active ingredient: atropine sulfate monohydrate 1.0%

Preservative: benzalkonium chloride 0.01%

Inactive ingredients: hypromellose, boric acid, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

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

(Attach proposed text)

16 HOW SUPPIED/STORAGE AND HANDLING

ISOPTO® Atropine [redacted] (b) (4) is supplied sterile in [redacted] (b) (4) low density polyethylene plastic DROP-TAINER® dispensers and [redacted] (b) (4) low density polyethylene tips with red polypropylene caps as follows.

5 mL filled in 8 mL bottles:
15 mL filled in 15 mL bottles: [redacted] (b) (4)

Storage: Store at 2 - 25°C.

Reviewer's Assessment: Pending

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Yes	See comment
Available units (e.g., bottles of 100 tablets)	Yes	5 and 15 ml Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	Acceptable
Special handling (e.g., protect from light, do not freeze)	Yes	Acceptable
Storage conditions	Yes	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Recommend:

16 HOW SUPPLIED/STORAGE AND HANDLING

ISOPTO® Atropine ((b) (4) 1%) is supplied sterile in low-density polyethylene plastic DROP-TAINER® dispensers with low-density polyethylene tips and polypropylene caps as follows:

- **5 mL filled in 8-mL bottles**
- **15 mL filled in 15-mL bottles**

(b) (4)

Storage: Store ISOPTO® Atropine 1% at 2–25°C (36–77°F).

Immediate Container Label

(b) (4)

Reviewer's Assessment: Pending

Reviewer's Information Request (6/27/2016) and Alcon's Response (7/12/2016):

Drug Product:

Issue 1.

The equivalency statement should be added in the label. The 1% strength is calculated based on amount of atropine sulfate monohydrate. For consistency with FDA's guidance on "Naming of Drug Products Containing Salt Drug Substances" and the USP Salt Policy, an equivalent statement for label, e.g.: *Each mL of atropine sulfate (1%) is equivalent to (contains) 8.3 mg of atropine should be included.

Response for Issue 1.

Alcon agrees and commits to update the packaging components prior to approval. Updated draft US PI text is submitted with in Module 1.14.

Issue 2.

Revise storage statement from (b) (4) to 2 to 25°C on container label and carton.

Response for Issue 2.

Alcon agrees and commits to update the packaging components prior to approval.

Issue 3.

On the container label and carton revise (b) (4) to hypromellose 0.5%.

Response for Issue 3.

Alcon agrees and commits to update the packaging components prior to approval.

Reviewer's Evaluation of Response: Pending

Alcon has agrees to make the requested changes to the immediate container label. The reviewer has not been provided the revised updated label. Furthermore Alcon list in the present label that hypromellose (b) (4). This is incorrect and should list purified water (b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided- see review comments	Acceptable

Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided-see review comments	Acceptable
Route of administration 21.CFR 201.100(b)(3))	Provided	Acceptable
Net contents* (21 CFR 201.51(a))	Provided	Acceptable
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided- see review comment	Pending revision
Lot number per 21 CFR 201.18	Provided	Acceptable
Expiration date per 21 CFR 201.17	Provided	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Acceptable
Storage (not required)	Provided	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Acceptable
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Acceptable
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.

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

**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.

Carton Labeling

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: Adequate

Reviewer's Information Request (6/27/2016) and Alcon's Response (7/12/2016):

Drug Product:

Issue 1.

The equivalency statement should be added in the label. The 1% strength is calculated based on amount of atropine sulfate monohydrate. For consistency with FDA's guidance on "Naming of Drug Products Containing Salt Drug Substances" and the USP Salt Policy, an equivalent statement for label, e.g.: *Each mL of atropine sulfate (1%) is equivalent to (contains) 8.3 mg of atropine should be included.

Response for Issue 1.
Alcon agrees and commits to update the packaging components prior to approval. Updated draft US PI text is submitted with in Module 1.14.

Issue 2.
Revise storage statement from (b) (4) to 2 to 25°C on container label and carton.

Response for Issue 2.
Alcon agrees and commits to update the packaging components prior to approval.

Issue 3.
On the container label and carton revise (b) (4) to hypromellose 0.5%.

Response for Issue 3.
Alcon agrees and commits to update the packaging components prior to approval.

Reviewer's Evaluation of Response: Pending
Alcon has agrees to make the requested changes to the carton label. The reviewer has not been provided the revised updated label. Furthermore Alcon list in the present label that hypromellose (b) (4). This is incorrect and should list purified water (b) (4)

The information is adequate to support approval from drug product perspective. Minor labeling changes/revisions are ongoing.

List of Deficiencies: None

Minor labeling revisions are ongoing. One outstanding IR for clarification an NDA correction

Requested a prompt written response by October 7, 2016

1. Please list hypromellose as an inactive ingredient (b) (4) (carton, immediate container label, and package insert).

2. In your response to Information Request dated 31 August 2016, you made reference to NDAs using the same red colorant, but continued to list as "(b) (4)" polypropylene closure in the text of the amendment, although in the updated Summary of Stability tables you describe as "red". Please clarify, and provide a statement that colorant in closure is the same as referenced.

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
9/27/2016

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

Balagee Shanmugam, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch III
9/27/2016

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Weight Change	Temperature excursions	M	Full 24-month shelf life data is within specification	Acceptable	Significant changes can affect trends in assay, BAC, and osmolality

List of Deficiencies

None outstanding

Primary Drug Product Reviewer Name and Date

Milton. J. Sloan, PhD
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
9/27/2016

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

Balagee Shanmugam, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch III
9/27/2016

Balajee Shanmugam

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Milton Sloan

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CHAPTER VII: Biopharmaceutics

NDA: 208151

Drug Product Name: Atropine sulfate ophthalmic solution

Strength(s): Atropine 1.0 %

Route of Administration: Ophthalmic

Proposed Indication: Treatment Cycloplegia, Amblyopia (b) (4), and for Pupillary dilation.

Applicant Name: Alcon Research, Ltd

Executive Summary:

The proposed drug product, Isotpo® Atropine 1.0%, is an ophthalmic solution containing 1.0 % w/v atropine sulfate as the active drug substance. The application is relying on the published literature for pharmacokinetics (PK), safety and efficacy of the proposed drug product.

The Applicant requested a waiver of the requirement to provide evidence of in vivo bioavailability (BA) or bioequivalence (BE) under 21 CFR 320.22(e) which states that the FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence. The Applicant submitted literature publication containing bioavailability data and the bridge between the formulation used in the publications with the PK information and the proposed drug product is adequate. The PK data will be reviewed by the Office of Clinical Pharmacology (OCP). Even though the Applicant submitted a biowaiver request under 21 CFR 320.22(e), the CFR 320.21 requirement for submission of bioavailability and/or bioequivalence data has been met by the provided literature information and therefore a biowaiver request is not needed.

From the Biopharmaceutics perspective there is an adequate bridge between some of the formulations used in the articles submitted to support PK, safety and efficacy and the proposed drug product.

From the Biopharmaceutics perspective, NDA 208151 for Isotpo® Atropine (atropine sulfate ophthalmic solution) 1.0%, is recommended for APPROVAL.

Submission:

Alcon submitted the current NDA for Isotpo® Atropine (atropine sulfate ophthalmic solution) 1.0% for ophthalmic use under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application is relying on the published literature for PK, safety and efficacy of the proposed drug product.

Biopharmaceutics:

Atropine sulfate ophthalmic solution, 1.0% is a sterile, preserved, multi-dose ophthalmic solution formulation containing 1.0 % w/v atropine sulfate as the active drug substance. The product has two presentations: a 5 mL fill in 8 mL round bottle and a 15 mL fill in 15 mL round bottle.

Atropine sulfate ophthalmic solution is an antimuscarinic agent that has been commercially available from several manufacturers in the United States for over 30 years. The product is intended for treatment of mydriasis and/or cycloplegia and for pupillary dilation desired in inflammatory conditions of the iris and uveal tract. The Applicant claimed that atropine can also be used for penalization of the healthy eye in the treatment of amblyopia (b) (4)

Table 1: Composition of atropine sulfate ophthalmic solution[1], 1.0%

Component	Percent W/V	Function/Purpose
Atropine Sulfate	1.0[a]	Active
Benzalkonium Chloride	0.01[b]	Preservative
Hypromellose	(b) (4)	
Boric Acid		
Hydrochloric Acid and/or Sodium Hydroxide	Target pH (b) (4)	pH Adjusting Agent
Purified Water	QS to 100	(b) (4)

[a]Adjusted for purity and water determination to equal 1.0% atropine sulfate monohydrate, equivalent to 8.3 mg/mL of atropine
[b]Adjust Benzalkonium chloride concentration based on assay value of the raw material or stock solution

The Applicant stated that the formulation development of the proposed drug product was based on the unapproved Isopto® Atropine 1.0% solution which has been manufactured and marketed by Alcon over 30 years in two configurations (5 mL: NDC 0998-0303-05, 15 mL: NDC 0998-0303-15).

Bridging the formulations described in the literature and the proposed drug product

The application is relying on the published literature for PK, safety and efficacy of the proposed drug product. Multiple studies [literature references] have been provided to support the clinical efficacy, safety, and human pharmacokinetics in this NDA submission. The cited studies critical to demonstrating PK, safety and efficacy of the proposed drug product are summarized in tables 2-5 below.

[1] In the original NDA submission [02/12/2016], the Applicant reported the target pH as (b) (4). The reported pH of three batches was pH 4.5, 4.6 and 4.5

Table 2: Studies critical to describe the human[2] pharmacokinetic profile of the proposed drug product

Literature reference	Kaila 1999	Lahdes 1988
Concentration of Atropine Evaluated	1%	1%
Formulation	1% atropine sulphate ophthalmic solution (Oftan Atropin 10 mg/ml eyedrops, Star Pharmaceuticals Tampere, Finland) Preservative-free, formulation lists only 1% atropine sulfate, water and hydrochloric acid as the only ingredients.	1% atropine sulphate ophthalmic solution (Oftan Atropin 10 mg/ml eyedrops, Star Pharmaceuticals Tampere, Finland) Preservative-free, formulation lists only 1% atropine sulfate, water and hydrochloric acid as the only ingredients.
Dose and duration of delivery	30 µl instilled unilaterally to the lower cul-de-sac of the eye	40 µl instilled to the lower cul-de-sac of one eye
Comparative chemical and physical measurements	No comparative testing conducted. Described differences not expected to lead to performance differences	No comparative testing conducted. Described differences not expected to lead to performance differences

Table 3: Studies critical to describe the safety profile of the proposed drug product

Literature reference	(b) (4) Fang 2010	(b) (4) PEDIG 2009	(b) (4) Song 2011
Concentration of Atropine Evaluated	0.025%	1%	0.25%, 0.5%, 1%
Formulation	Diluted 0.25% atropine sulfate ophthalmic solution Wu-Fu lab Co., Ilan Taiwan with distilled water 1:10 Excipients: Benzalkonium chloride, Edetate disodium, Sodium chloride, Citric acid, Borax, Purified water.	No details provided	No details provided
Dose and duration of delivery	Once nightly at bedtime for 12 months	One drop in the sound eye each weekend day for 16 weeks	Once daily or every other day for 6 to 24 months
Comparative chemical and physical measurements	No comparative testing conducted. Described differences not expected to lead to performance differences	No information available and therefore comparison not possible	No information available and therefore comparison not possible

[2] Systemic bioavailability of ocularly applied 1% atropine eye drops [Kaila *et al*] was investigated in six healthy human subjects. Landes *et al* reported using sixteen hospitalized patients to investigate systemic absorption of topically applied ocular atropine.

Table 4: Studies critical to describe the efficacy of the proposed drug product in Cycloplegia/Mydriasis

Literature reference	Celebi 1999	Ebri 2007	Liu 2012	Caruba 2006	McCormick 2006	Barbee 1957
Concentration of Atropine Evaluated	1%	1%	1% eye ointment	1%	1%	1%
Formulation	No details provided	No details provided	No details provided Shenyang Xingqi Pharmaceutical Co Ltd. Directions for Use available	No details provided	No details provided	No details provided
Dose and duration of delivery	3 times daily for 3 days; single morning instillation on 4th day	one drop three times daily for 3 days	3 times daily for 3 days	One drop the day before intervention and 1 drop on the day of intervention	2 drops to lower conjunctival fornix or 2 drops to pledget applied to inferior fornix for 20 min	3 drops in one eye
Comparative chemical and physical measurements	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible

Table 5: Studies critical to describe the efficacy of the proposed drug product in Amblyopia/ (b) (4)

Literature reference	(b) (4)	PEDIG 2008	Repka 2014	Foley-Nolan 1997	PEDIG 2005	Tejedor 2008*
Concentration of Atropine Evaluated		1%	1%	1%	1%	1%
Formulation		No details provided	No details provided	No details provided	No details provided	Colircusi Atropina 1%; AlconCusi, Barcelona, Spain
Dose and duration of delivery		each weekend day in sound eye for 5 weeks, increased to 1 drop daily for 12 weeks in some patients	1 drop daily for 6 months	One drop daily each morning for an average of 7.2 months	1 drop daily for the sound eye Duration was variable with a minimum of 6 weeks	Twice weekly when interocular acuity difference was present and once weekly for maintenance therapy up to 6 months
Comparative chemical and physical measurements		No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No information available and therefore comparison not possible	No direct comparison conducted.

The Applicant stated that some of the literature references do not provide any details of the composition of the formulation or any comparative chemical and physical measurements. Two literature references [(b) (4) supporting the (b) (4)] used an identical marketed 1.0% Atropine formulation that matches the drug product that is being proposed in this NDA. The drug product used

(b) (4)

in the study, reported by [redacted] (b) (4)

Tejedor et al 2008 used a legacy Alcon 1.0% atropine formulation that was manufactured in Barcelona Spain. This formulation had the same concentration of atropine as the proposed NDA formulation. The comparison of these formulations is provided in table 6 below:

Table 6: Comparison of the proposed formulation and the formulations used in some of the reported literature[5].

Ingredient	**Proposed NDA Formulation FID10028 % w/v**	(b) (4)	Alcon Cusi Formulation **FID96218** (Tejedor 2008)
Atropine Sulfate	1.0		1.0
Benzalkonium Chloride	0.01		-
Methylparaben	(b) (4)		0.03
Propylparaben			0.02
Hypromellose (b) (4			-
Boric Acid			-
Sodium Chloride			0.38
Disodium Phosphate			0.05
Monopotassium Phosphate, Hydrate			0.84
Hydrochloric Acid and/or Sodium Hydroxide	pH Adjustments to target value of (b) (4)		pH Adjustments to target value of 5.4
Purified Water	QS to 100%		QS to 100%

The Applicant claimed that regardless of the atropine formulation referenced in each study, and despite the differences in patient populations and study designs, the results of each study are directionally similar and support the safety and efficacy of atropine for each proposed indication. It is the Applicant's position that the referenced literature is representative of the safety and efficacy of the proposed atropine formulation.

Biowaiver Request:

This NDA is a 505(b)(2) application which relies solely on published literature to support the drug product's safety and efficacy. The Applicant requested the waiver of the requirement to provide evidence of in vivo bioavailability (BA) or bioequivalence (BE) under 21 CFR 320.22(e), which states that the FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health.

[4] Drug product manufacturing facility for the formulation proposed in the current NDA

[5] Note: In the original NDA submission [02/12/2016], the Applicant reported the target pH as (b) (4). The reported pH of three batches was pH 4.5, 4.6 and 4.5. In a response to information request [05/05/2016], for the proposed NDA formulation, the Applicant reported the target pH as (b) (4). The pH reported for the stability batches, under various stability conditions, was 3.78 to 4.75. Therefore, the Reviewer believes that the target value of pH (b) (4) reported above in table 6 may be a typographical error.

Reviewer's Assessment:

The proposed product is a clear, colorless to [redacted] aqueous solution formulated at a pH of approximately [redacted] and is isotonic (osmolality between 285-295 mOsm/kg). Besides the active drug substance, atropine, the formulation contains additional excipients. Hypromellose [redacted], a cellulosic polymer, is used as a [redacted]; boric acid is used as a [redacted] and benzalkonium chloride is used as a preservative. In this Reviewer's opinion, none of these additional excipients are likely to significantly affect the pharmacokinetic profile of atropine when used via the ophthalmic route.

Atropine ophthalmic solution has been used for pupillary dilation and cycloplegia for over 100 years. The drug product causes local and systemic anticholinergic effects. As per the clinical review the proposed product is dosed topically to the cornea and has been demonstrated to penetrate the cornea directly to the site of action (iris and ciliary body)[6].

The Applicant submitted literature references [Kaila et al and Lahdes et al] providing the PK information for 1% atropine solution. The comparison of the formulation [Star Pharmaceuticals] reported in the two articles that provide the PK information and the proposed drug product formulation is presented in table 7 below. The formulation of 1% atropine solution, reported in these articles supporting PK information, is slightly different from the proposed product formulation. In this Reviewer's opinion these formulation differences are minor and not likely to affect the systemic PK profile of atropine. Therefore, the bridge between the formulation used in the publications with the PK information and the proposed drug product is adequate.

Even though the Applicant submitted the biowaiver request under 21 CFR 320.22(e), the CFR 320.21 requirement for submission of bioavailability and bioequivalence data has been met by the provided literature information and therefore a biowaiver request is not needed.

Table 7: Comparison of the formulation [Star Pharmaceuticals] reported in articles supporting PK and the proposed drug product

Component	% W/V	
	Proposed product	Oftan Atropine eye drops, Star Pharmaceuticals[7]
Atropine Sulfate	1.0	1.0
Benzalkonium Chloride	0.01	-
Hypromellose	[redacted]	-
Boric Acid		-
HCl or NaOH		-
HCl		QS
Purified Water	QS	QS

For the efficacy and the safety information, several of the literature references do not

[6] DARRTS: NDA-208151: REV-CLINICAL-21(Primary Review): Original-1: 09/13/2016: CHAMBERS, WILEY A

[7] Kaila et al: Acta Ophthalmol. Scand. 1999: 77: 193–196

provide details of the composition of the formulation or any comparative chemical and physical measurements; however, most of the reported literature formulations used 1.0% atropine. Even though there may be minor formulation differences in the various 1.0% atropine solution formulations, these differences are not likely to affect the absorption and distribution of atropine in the eye. In addition, as noted by the Clinical Reviewer, it is likely that many of these publications used the unapproved Alcon 1% atropine solution. From a Biopharmaceutics perspective, the formulations used in the Kaila et al, 1999, Lahdes et al, 1980, (b) (4) Tejedor et al, 2008 and Fang et al, 2010 publications are adequately bridged to the proposed drug product.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 208151 for Isotpo® Atropine sulfate ophthalmic solution, 1.0%, is recommended for **APPROVAL.**

Om Anand, Ph.D. [Date: 09/30/2016]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

I concur with Dr. Om Anand's assessment and recommendation.

Elsbeth Chikhale, Ph.D. [Date: 09/30/2016]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Elsbeth Chikhale

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Om Anand

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FACILITIES

Product Background:

NDA/ANDA: 208151

Drug Product Name / Strength: Atropine Ophthalmic Solution, 1%

Route of Administration: Ophthalmic Solution

Applicant Name: Alcon Research Ltd.

Review Summary: *Atropine Sulfate Ophthalmic Solution, 1%, is a sterile, preserved, multi-dose aqueous ophthalmic solution. Two presentations are proposed - 5 mL in 8 mL round LDPE bottle and 15 mL in 15 mL round LDPE bottle, with 15 mm flat tip LDPE* (b) (4) *and 15 mm PP red* (b) (4) *closure. The product has been manufactured and was marketed by the applicant for over 30 years. The review of facilities supporting the submission has been completed and at this time, there appear to be no significant risks to drug product quality based on evaluation of compliance and inspectional history. No preapproval inspections were deemed necessary to support the submission. All the facilities are determined acceptable to support approval of NDA-208151 at this time.*

List of Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original	02/12/2016
Amendments - Quality Information	5/5/2016, 5/12/2016, 7/12/2016, 8/31/2016, 9/14/2016, 9/16/2016

Highlight Key Outstanding Issues from Last Cycle: None, original review.

Concise Description Outstanding Issues Remaining: None..

3.2.S.2 Manufacture

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Comparability Protocols

None submitted

Reviewer's Assessment: Not applicable.

Post-Approval Commitments

None submitted

Reviewer's Assessment: Not applicable.

Lifecycle Management Considerations

None identified.

List of Deficiencies: None

Primary Facilities Reviewer Name and Date: Vidya Pai, 09/23/216, OPF/DIA/B3,

Secondary Reviewer Name and Date: Derek S. Smith, Ph.D. 10/5/2016

Derek Smith

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Vidya Pai

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MICROBIOLOGY

Product Background: Currently marketed unapproved product

NDA: 208-151

Drug Product Name / Strength: ISOPTO ATROPINE 1%

Route of Administration: Topical ophthalmic

Applicant Name: Alcon Research Ltd.

Manufacturing Site: Alcon Research, Ltd
Fort Worth, TX
FEI Number: 1610287

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed (table):

Submission	Date Received
Original NDA submission	12 February 2016
Quality Response to Information Request	12 May 2016
Quality Response to Information Request	19 September 2016

Supporting Documents:

NDA micro review 208135.doc, 25 January 2016 reviewed (b) (4) the filling equipment, (b) (4) sterilization of equipment, container closure component (b) (4), and container closure component (b) (4) sterilization.

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: There are no outstanding issues, the application is recommended for approval from a quality microbiology perspective.

S Drug Substance – NA

Reviewer's Assessment: Drug substance is not sterile; this section was not reviewed.

P.1 Description of the Composition of the Drug Product

Description of drug product – The drug product is a sterile topical ophthalmic multi-use solution. It has two presentations, 5 mL fill in 8 mL round bottle and a 15 mL fill in 15 mL round bottle.

Drug product composition – Composition of the drug product is as follows:

Component	Percent W/V	Function/Purpose
Atropine Sulfate	1.0	Active
Benzalkonium Chloride	0.01	Preservative
Hypromellose Boric Acid Hydrochloric acid and/or	(b) (4)	
Sodium Hydroxide	Target pH (b) (4)	pH Adjusting Agent
Purified Water	QS to 100	Vehicle

Description of container closure system – LPDE DROP-TAINER

8 and 15 mL (b) (4) low density (LDPE) round bottle
15mm (b) (4)
15mm (b) (4) Polypropylene closure

Note: The bottle and (b) (4) are sterilized by (b) (4) and the closure is sterilized by (b) (4). This container closure Drop-Trainer system is approved and used in numerous ophthalmic products manufactured by Alcon (see NDA 208-135).

Reviewer's Assessment: The information provided is adequate.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure Integrity (CCI):

CCI was demonstrated by microbial ingress studies. Microbial immersion challenge test was performed for both sized bottles on media filled units. [redacted] Three studies were performed on the 8 mL bottle size; all studies met the acceptance criteria and demonstrate the ability of the container closure to exclude microorganisms. The 15 mL and 8 mL have the same neck dimensions and they use the same [redacted] and closure, therefore the container closure integrity testing on the 8 mL bottle is applicable to the 15 ml bottle.

Reviewer's Assessment: The data provided supports the ability of the container closure to exclude microorganisms at the time of manufacture. The CCI over the shelf life of the product is addressed in the stability program.

Antimicrobial Effectiveness Testing (AET):

AET studies were provided for the full strength product and product on stability. The sponsor did not provide AET studies to support the lowest acceptable preservative concentration. This information was requested and was provided by the sponsor on 12 May 2016. The AET studies provided were the following:

TDOC-0018739: Microbial recovery/enumeration validation
TDOC-0050964 PET study for 85% of label claim for one lot
TDOC-0018791 PET study 100% label claim for 6 product lots
TDOC-0018792 PET at 52 weeks stability time point for 6 product lots

Note: AET studies are also called Preservative Effectiveness Testing (PET).
Note: The preservative specification is [redacted]% of label claim.

The studies were performed following USP <51>. The enumeration validation demonstrated count recovery of ≥ [redacted]% of the diluent control supporting the ability of the neutralizer system to recover low counts and thereby supports the data in the AET studies. The AET studies provided bracket the label claim concentrations of the preservative and support the

effectiveness of the preservative through the shelf life of the proposed drug product. The acceptance criteria are as follows :

(b) (4)

All studies met the acceptance criteria.

Reviewer's Assessment – All studies met the acceptance criteria and support the effectiveness of the preservative used in the drug product over part of the shelf life of the proposed product (up to (b) (4)). A commitment to test the product at expiry was sent on 09 September 2016. (Response due by 9/16)

Information request:
We acknowledge the four documents provided for the Antimicrobial Effectiveness Testing (AET also called PET) for the proposed product, namely TDOC-0018739 (Microbial recovery/enumeration validation), TDOC-0050964 PET study for 85% of label claim, TDOC-0018791 PET study for 100% label claim, and TDOC-0018792 PET at 52 weeks stability time point. We also acknowledge that these are developmental studies only, and therefore not included in the stability protocol. The protocol for the AET development study could not be located in the submission, and it was not clear as to whether or not there is an AET testing time point for the developmental batches at the end of shelf life. Confirm that AET studies will be performed for at least one batch of the drug product at the end of shelf life as specified in ICH Q1A Stability Testing of New Drug Substances and Products.

Response 19 September 2016: The report for the AET testing at the 104 week time point for stability lots 18952-01, 18952-03, 18953-01, 18953-02, and 08953-03 stored at 25°C/40% RH was provided. The testing was per USP <51> and met the acceptance criteria.

Review of response: The response is acceptable. The sponsor provided the 104 week time point AET data for 6 lots of product that support the effectiveness of preservative system over the shelf life of the product.

P.3 Manufacture

P.3.1 Manufacturers

Drug Product Manufacturer

Alcon Research Ltd.
ASPEX (Alcon Sterile Product Expansions) Manufacturing Facility
6201 South Freeway
Fort Worth Texas 76134

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

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

P. 8.1 Stability Summary and Conclusion

The sponsor provided 78 weeks of stability data for 6 lots; three lots per configuration. There were no failures reported.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor states that the three primary stability batches were produced at commercial scale in the manufacturing facility. The ongoing stability studies for these three lots will continue until protocol completion. Thereafter, at least one lot will be placed on long term stability. Any lots to fall outside the approved specifications that affect safety or efficacy will be promptly withdrawn from the market and reported to the Agency.

P.8.3 Stability Data

Lots 18952-01, 18952-02, and 18952-03 (5 mL in 8 mL Drop-Tainer)

Lot 18953-01, 18953-02, and 18953-03 (15 mL in 15 mL Drop-Tainer)

Data for all 6 lots were initially provided for up to the 78 week time point. There were no failures for the sterility testing performed at the 26 and 52 week time points. Preservative effectiveness testing was also performed on all six lots at the 52 week time point and met the acceptance criteria; the AET was performed as a developmental test and will not be used in the routine stability program. The applicant subsequently (Sept 19, 2016 amendment) provided USP <51> AET testing results for the 104 week time point for stability lots 18952-01, 18952-03, 18953-01, 18953-02, and 08953-03 stored at 25°C/40% RH. All stability lots met the USP <51> acceptance criteria. (See Section P.2.5 above.)

Reviewer's Assessment: The stability program is acceptable for a topical ophthalmic product, data provided to date is acceptable.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Since there are no materials of biological origin, there is little risk of the product for the presence of adventitious agents.

Reviewer's Assessment: Acceptable.

R Regional Information

Executed Batch Records

Reviewer's Assessment: Executed batch record for Lot 227515F was provided in the submission. This was a (b) (4) kg batch manufactured in October 2013 and was a primary stability batch.

Comparability Protocols

There were no comparability protocols submitted.

Reviewer's Assessment: NA

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

2.A. Package Insert

Dosage is one or two drops in the eye up to four times daily. Section 17.4 Handling includes the warning that patients are to advised not to touch the dispenser tip to any surface as this may contaminate the solution.

Reviewer's Assessment: There are no microbiology concerns for the label.

Post-Approval Commitments: None

Reviewer's Assessment: NA

Lifecycle Management Considerations: None

Reviewer's Assessment: NA

List of Deficiencies: None

QUALITY ASSESSMENT

Primary Microbiology Reviewer Name and Date:

Denise A. Miller 23 September 2016
Sr. Microbiology Reviewer
OPQ/OPF/DMA/Branch II

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

Neal J. Sweeney, Ph.D. 24 September 2016
Microbiology Quality Assessment Lead (Acting)
OPQ/OPF/DMA/Branch II

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 9/27/2016 10:37:34AM
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Denise Miller

Digitally signed by Denise Miller
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Chunchun Zhang

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