CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208151Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208151 SUPPL # HFD #

Trade Name: Isopto Atropine

Generic Name: Atropine Sulfate Ophthalmic Solution, 1%

Applicant Name: Alcon Research, Ltd.

Approval Date, If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21146 Atropine Sulfate Injection

NDA# 206289 Atropine Sulfate Ophthalmic Solution

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☒ NO ☐

If yes, explain: This is a 505(b)(2) literature only NDA application.

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1-

(b) (4)

YES ☐ NO ☒

Investigation #2-

(b) (4)

YES ☐ NO ☒

Investigation #3-

Salazar M	Iris Pigmentation and Atropine Mydriasis	J Pharm Exp Therapeutics 197(1):79-88	1975

YES ☐ NO ☒

Investigation #4-

Arnold RW	Duration and Effect of Single Dose Atropine: Paralysis of Accommodation in Penalization Treatment of Functional Amblyopia	Binocular Vision & Strabismus Quarterly; 19(2):81-86.	2004

YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such

investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1-

	(b) (4)

YES ☐ NO ☒

Investigation #2-

	(b) (4)

YES ☐ NO ☒

Investigation #3-

Salazar M	Iris Pigmentation and Atropine Mydriasis	J Pharm Exp Therapeutics 197(1):79-88	1975

YES ☐ NO ☒

Investigation #4-

Arnold RW	Duration and Effect of Single Dose Atropine: Paralysis of Accommodation in Penalization Treatment of Functional Amblyopia	Binocular Vision & Strabismus Quarterly; 19(2):81-86.	2004

YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

No new clinical trials were submitted. This is a literature only application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 No clinical investigations conducted by applicant

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1-

(b) (4)

YES ☐ NO ☒

Investigation #2-

(b) (4)

YES ☐ NO ☒

Investigation #3-

Salazar M	Iris Pigmentation and Atropine Mydriasis	J Pharm Exp Therapeutics 197(1):79-88	1975

YES ☐ NO ☒

Investigation #4-

Arnold RW	Duration and Effect of Single Dose Atropine: Paralysis of Accommodation in Penalization Treatment of Functional Amblyopia	Binocular Vision & Strabismus Quarterly; 19(2):81-86.	2004

YES ☐ NO ☒

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Michael Puglisi
Title: Regulatory Project Manager

Name of Division Director signing form: Wiley Chambers
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL J PUGLISI
12/09/2016

WILEY A CHAMBERS
12/09/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208151 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Isopto Atropine Established/Proper Name: atropine sulfate Dosage Form: ophthalmic solution		Applicant: Alcon Research, ltd. Agent for Applicant (if applicable):
RPM: Michael Puglisi		Division: DTOP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action • User Fee Goal Date is 12/12/16	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
• Copies of all action letters *(including approval letter with final labeling)*	In Package
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
• Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	6/2/16 6/1/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 6/8/16 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 11/7/16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/1/16 ☐ Not a (b)(2) 11/9/16
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: _____	7/13/16
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	In Package
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	In Package
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 2/11/13
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/1/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/30/16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	4/4/16, 9/13/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	Addressed in 9/13/16 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 11/8/16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5/16/16, 11/9/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4/11/16, 11/7/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 10/12/16, 11/10/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	In 10/12/16, Integrated Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, July 27, 2016 8:46 AM
To: 'Nitschmann, Paul'
Subject: Nonclinical Information Request - IND 208151

Hi Paul,

Below please find an information request from our nonclinical reviewer for the atropine NDA. Please confirm receipt and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

1. *A thorough search of published literature should be performed regarding the nonclinical general toxicology and reproductive toxicology of atropine. Please identify any key words used. For example, the following articles are representative of relevant literature that could be submitted to support the NDA:*
    - *Boyd, C., and E. Boyd, 1962, "The chronic toxicity of atropine administered intramuscularly to rabbits", Toxicol Appl Pharmacol, 4: 457 – 467.*
    - *Lulham, G., et al., 1990, "A subchronic toxicity study of two inhaled aerosolized atropine sulfate formulations in rats and dogs", Drug Chem Toxicol, 13(1): 19 – 42.*
    - *Ratnasooriya, W., 1989, "Effects of atropine on fertility of male rats", Vidyodaya J, Sci, 1: 47 – 55.*
    - *Ban, Y., et al., 2002, "Impairment of male fertility induced by muscarinic receptor antagonists in rats", Reprod Toxicol, 16: 757 – 765.*
    - *Sato, T., et al., 2005, "Atropine-induced inhibition of sperm and semen transport impairs fertility in male rats", J Toxicol Sci, 30: 207 – 212.*
    - *Schlough, J., 1969, "Delayed implantation in the rat induced by atropine", Biol Reprod, 1: 315 – 319.*
    - *Patil, M., et al., 2009, "Atropine sulfate induced changes in uterine, adrenal, liver and thyroid gland in female albino rats", J Pharmacol Toxicol, 4: 236 – 245.*
    - *Dziuk, P., and T. Mann, 1963, "Effect of atropine on the composition of semen and secretory function of male accessory organs in the boar", J Reprod Fertil, 5: 101 – 108.*
    - *Black, D., and R. Duby, 1965, "Effect of oxytocin, epinephrine, and atropine on the oestrous cycle of the cow", J Reprod Fertil, 9: 3 – 8.*

2. *Please also identify any listed drug(s) described in the submitted published literature (e.g., trade name(s)). Reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s).*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL J PUGLISI
07/27/2016

PeRC Meeting Minutes
July 13, 2016

PeRC Members Attending:
Lynne Yao
Gettie Audain
Wiley Chambers
Robert "Skip" Nelson
Gerri Bauer
Lily Mulugeta
Hari Cheryl Sachs
Barbara Buch
Adrienne Hornatko-Munoz
Jackie Yancy
Greg Reaman
Ruthie Davi
Peter Starke
Meshaun Payne
John Alexander
Raquel Tapia
Thomas Smith
Ikram Elayan
Lisa Falcon
Dionna Greene

Agenda

9:00	NON-RESPONSIVE				
9:30					
9:45					
10:05	NDA 208151	Isopto Atropine 1%(atropine sulfate) Opthalmic Solution (Assessment)	DTOP	Michael Puglisi	(1) For mydriasis, (2) cycloplegia , (3) penalization of the healthy eye in treatment of amblyopia, (b) (4)
10:25	NON-RESPONSIVE				
10:45					
11:00					
11:10					

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NON-RESPONSIVE

Isopto Atropine 1% (atropine sulfate) Opthalmic Solution (Assessment)

- Proposed Indication: (1) For mydriasis, (2) cycloplegia, (3) penalization of the healthy eye in treatment of amblyopia, (b) (4)
- (b) (4)
- The division further clarified that this is a marketed unapproved drug.
- The PDUFA goal date is December 12, 2016.
- *PeRC Recommendations*:
  - The PeRC agreed to the approval of a fully assessed product but not labeled for less than 3 months of age because of the concern of adverse events with systemic absorption in infants < 3 months of age.

3 Pages has been Withheld as Non-Responsive immediately following this page

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/s/

GETTIE AUDAIN
08/10/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208151

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

ATTENTION: Paul Nitschmann, M.D.
Head, BD&L and Early Development Regulatory Affairs

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) dated February 12, 2016, received February 12, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Atropine Sulfate Ophthalmic Solution, 1%.

We also refer to:

- your March 9, 2016, correspondence, received March 9, 2016, requesting review of your proposed proprietary name, Isopto Atropine
- and your May 10, 2016, amendment, received May 10, 2016, to your request for name review

We have completed our review of the proposed proprietary name, Isopto Atropine, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Michael Puglisi, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
06/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208151

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D.
Head, BD&L and Early Development Regulatory Affairs
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) dated and received February 12, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Isopto Atropine 1% (atropine sulfate ophthalmic solution).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application will be considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 12, 2016**.**

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by the week of November 12, 2016, approximately.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION
Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage

you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
04/12/2016

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, April 06, 2016 10:40 AM
To: 'Nitschmann, Paul'
Subject: Quality Reviewer's Comments - NDA 208151

Hi Paul,

Below please find comments from our Quality reviewer for the Isopto Atropine NDA, which was submitted on February 12, 2016. Please confirm receipt and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Quality Reviewer's Comments:

Since your NDA submission relies on numerous studies from the published literature, the FDA's acceptance of the provided published literature data as evidence of satisfying the PK, safety, and efficacy CFR's requirements is contingent on the appropriateness of the scientific bridge between the drug product(s) used in the literature studies using ophthalmic administration and the formulation of your proposed drug product. Therefore, the supporting information should contain enough details to allow FDA the evaluation of the bridging of these products. For this purpose, provide a table with columns describing the following:

a. Each cited study critical to demonstrating the safety and efficacy of your proposed drug product,

b. Each cited study critical to describe the pharmacokinetic profile of the proposed drug product.

c. Precise composition of the administered drug product in the cited study,

d. Administered dose and duration of delivery in the cited study,

e. Comparative chemical and physical measurements such as osmolality, pH, etc. of the solutions (proposed vs. those used in the cited published literature articles),

f. Bridging justification: Where the administered drug product in your cited study differs from your proposed drug product, provide a justification why you can extrapolate its results to the expected clinical response from the administration of your proposed drug product.

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/s/

MICHAEL J PUGLISI
04/06/2016

Puglisi, Michael

From: Puglisi, Michael
Sent: Thursday, March 24, 2016 4:18 PM
To: 'Nitschmann, Paul'
Subject: Quality Microbiologist's Comments - NDA 208151

Hi Paul,

Below please find comments from our Quality Micro reviewer for the Isopto NDA, which was submitted on February 12, 2016. Please confirm receipt and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Quality Microbiologist Comments:
We acknowledge the Preservative Effectiveness data provided for the 6 stability lots in the submission. From the provided summary, it appears that none of the six lots were manufactured at or below the lower limit for the concentration of the preservative. This does not demonstrate that the preservative is effective for lots manufactured at the lower limit. Provide a one-time preservative effectiveness study for the formulation with the preservative at or below the lowest acceptable concentration.

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/s/

MICHAEL J PUGLISI
03/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208151

NDA ACKNOWLEDGMENT

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D.
Head, BD&L and Early Development Regulatory Affairs
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Isopto (atropine sulfate ophthalmic solution) 1%

Date of Application: February 12, 2016

Date of Receipt: February 12, 2016

Our Reference Number: NDA 208151

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 12, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

MICHAEL J PUGLISI
02/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND (b) (4)
PIND 115869

MEETING MINUTES

Alcon Research, Ltd.
Attention: C. Brad Wooldridge
Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Wooldridge:

Please refer to your Pre-Investigational New Drug Applications (PIND) files for PIND (b) (4) and PIND 115869 ISOPTO atropine (atropine sulfate ophthalmic solution).

We also refer to the teleconference between representatives of your firm and the FDA on February 11, 2013. The purpose of the meeting was to gain concurrence from the Agency on a development plan that will lead to reviewable NDAs for (b) (4) and ISOPTO Atropine, 1%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	February 11, 2013, 1:00-2:00 PM, EST
Meeting Format:	Teleconference
Application Number:	(b) (4) and 115869
Product Name:	(b) (4) and ISOPTO Atropine, 1%
Sponsor/Applicant Name:	Alcon Research, Inc.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Judit Milstein

FDA ATTENDEES

Renata Albrecht, Division Director
Wiley A. Chambers, Deputy Director
William Boyd, Clinical Team Leader
Rhea Lloyd, Medical Officer
Martin Nevitt, Medical Officer
Lucious Lim, Medical Officer
Aaron Ruhland, Pharm/Tox Reviewer
Lori Kotch, Pharm/Tox Team Leader
Abel Eshete, Statistics Reviewer
Yan Wang, Statistics Team Leader
Yongheng Zhang, Clinical Pharmacology Reviewer
Gerlie Gieser, Clinical Pharmacology Reviewer
Balajee Shanmugam, CMC Lead
Judit Milstein, Chief Project Management Staff
Kathleen Joyce, Regulatory Counsel, Office of Unapproved Drugs and Labeling Compliance, (OUDLC)
Charles Lee, Senior Medical Advisor, OUDLC
Lori Cantin, Consumer Safety Officer, OUDLC
Shelleaha Nippoldt, Pharmacy Student, OUDLC

SPONSOR ATTENDEES

Terry J. Dagnon, U.S. and Canada, Head of Regulatory Affairs
Richard Reese, Global Project Regulatory Manager, External Diseases and Exploratory Projects
Michael Brubaker, Therapeutic Unit Head, External and Infectious Diseases
James Wheeler, Project Head, Pharmaceutical Development
Michela Palmer, Clinical Leader, Clinical Trial Management
Barry Astroff, Sr. Project Toxicologist, Preclinical Safety
Allan Weber, Sr. Project Pharmacokineticist
Dr. Lisa Stevenson, Associate Director, Pharma Safety Evaluation and Risk Management
Bhagwati Kabra, Head, CMC Teams
Adeniyi Adewale, Therapeutic Area Lead Statistician, External Diseases

1. BACKGROUND

The sponsor plans to develop [redacted] and ISOPTO Atropine 1% as two separated 505(b)(2) applications, and requested two PIND meetings to gain concurrence with the Agency on the development plan that will lead to reviewable NDAs for each one of the products.
On February 6, 2013, the Division sent preliminary comments on the questions posted in the briefing documents dated January 11, 2013.

As the questions posted in the corresponding briefing documents were similar for each PIND, the discussions reflected in these minutes, grouped by discipline, apply identically to both PINDs, unless in those instances where the difference is indicated. In addition, unless specifically addressed in these minutes, the sponsor agreed with the detailed preliminary responses sent by the Division on February 6, 2013.

2. DISCUSSION

Regulatory

The Division reiterated that it was unlikely that either of the two NDAs [redacted] based on the fact that there is likely sufficient data available in the literature to support its approval without additional clinical trials. The Division also stated that based on current literature, it is unlikely that those indications would [redacted]

The Division stated that there is likely sufficient information in literature to file literature only 505(b)(2) applications. In response to a sponsor's question, the Division stated that book chapters could not be used in lieu of adequate and well-clinical studies, but that the information provided in those books could be use for labeling purposes (e.g., onset and duration of action).

The Office of Compliance stated that they were not aware of any regulations addressing "equivalent products without a corresponding NDA should be [redacted] and that FDA follows a Compliance Policy Guide (CPG) regarding unapproved marketed drugs. This CPG describes the Agency's intent regarding enforcement action against unapproved drugs once a firm obtains approval.
The Office of Compliance further stated that although FDA intends to take enforcement action against unapproved drugs once a firm obtains approval, FDA considers many factors before taking such action (see language from CPG in section 4 below). These factors include the impact on patients who take the drug; the ability of the approved firm to supply the market; and the firms' GMP compliance.

Quality

The Agency reiterated the need to provide 12 month stability data at the time of submission.
The sponsor clarified that they have 10 years of stability data, at the same facility, with no change in formulation. The Agency acknowledged this clarification but further stated that for the historical lots the degradants were not analyzed, and therefore, impurity profiles and stereoisomers purity was unknown.

The sponsor proposed to file the applications with only 6 month of stability data on 2 primary stability batches, using the data on historical batches as supporting information. They also intend to generate additional impurity data from the ongoing supportive stability lots. The Agency

invited the sponsor to request a CMC meeting to further discuss this requirement once this data is generated.

Pharmacokinetic
The sponsor clarified that clinical pharmacology data of (b) (4) can be found on the last page of the bioanalytical literature reference (b) (4) included in the (b) (4) briefing document.

(b) (4)

A biowaiver request should be considered for ISOPTO atropine NDA since it appears that there is sufficient literature information to describe the systemic pharmacokinetics of atropine following topical ocular instillation.

Clinical
The Division stated that it believes that there is likely to be sufficient literature information to support a claim for (b) (4) and for mydriasis and cyclopegia for ISOPTO atropine, and therefore, no additional clinical studies are likely to be needed.

3. ISSUES REQUIRING FURTHER DISCUSSION
None

4. ADDITIONAL POST-MEETING COMMENTS
The following excerpts from the Marketed Unapproved Drugs GCP are provided by the Office of Compliance to support statements made during the meeting.

FDA can not disclose information on possible future enforcement actions on unapproved marketed drugs. The Marketed Unapproved Drugs Compliance Policy Guide (CPG) lists the risk based enforcement priorities used by the Agency when determining whether to take an enforcement action against unapproved drugs on the market before September 19, 2011. The CPG articulates the Agency's enforcement policy with regard to situations where one firm secures approval for a product that others are marketing without approval (see CPG section III.C, Special Circumstances – Newly Approved Product). Those drugs entering the market after September 19, 2011, will be immediately subject to enforcement action without consideration of these priorities.

Under our CPG, FDA generally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed; (3) the difficulty associated with conducting any required

studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first cease manufacturing unapproved forms of the drug product, and later cease distributing the unapproved product.

A firm seeking approval should be able to meet the needs of patients taking the drug and comply with current good manufacturing practice regulations.

5. ACTION ITEMS

The Division will issue minutes of the meeting within 30 days.
The sponsor will provide additional literature references in support of (b) (4)

The sponsor will generate additional (b) (4) and provide this information to the Agency with a request for a CMC meeting.

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/s/

WILEY A CHAMBERS
02/28/2013