

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206289Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206289 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Atropine sulfate ophthalmic solution Dosage Form: ophthalmic solution, 1%		Applicant: Akorn, Inc. Agent for Applicant (if applicable):
RPM: Christina Marshall		Division: DTOP
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ This application does not rely upon a listed drug. ☒ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: 7/18/14 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 <u>April 30, 2014</u> <u>Approval date: July 18, 2014</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☐ None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

❖ 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	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 7 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Breakthrough Therapy designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ 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 BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other-Information advisory

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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Not submitted ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action-Approval-July 18, 2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	April 25, 2014
• Original applicant-proposed labeling	October 23, 2013
• Example of class labeling, if applicable	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ 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.	
Original applicant-proposed labeling	
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	Yes
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Applicant did not require proprietary name for this product
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM Dec. 23, 2013 ☒ DMEPA March 11, 2014 ☐ DMPP/PLT (DRISK) ☒ OPDP April 9, 2014 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review: Dec. 23, 2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	Cleared by the (b)(2) Committee: March 31, 2014
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)-No exclusivity applies as this is a literature only NDA	☐ Not a (b)(2) ☐ Included This is a literature only NDA
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC July 9, 2014 ____ If PeRC review not necessary, explain: ____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	March 28, 2014 March 14, 2014 February 3, 2014 December 18, 2013 December 12, 2013 December 3, 2013 November 6, 2013
❖ Internal memoranda, telecons, etc.	May 15, 2014
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☒ No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
• Pre-NDA/BLA meeting- May 21, 2013	<i>Pre IND/PreNDA meeting held on May 21, 2013 (PIND 118218)</i>
• EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☒ July 18, 2014
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☒ June 27, 2014
PMR/PMC Development Templates <i>(indicate total number)</i>	☒ None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	Review: July 17, 2014 April 7, 2014 Filing Review: December 17, 2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☒ 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 <i>(indicate date of review/memo)</i>	Yes-Review dated July 15, 2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☒ Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Review(s) (<i>indicate date for each review</i>)	Review: March 12, 2014 Filing Review: February 28, 2014 and February 25, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None Review: April 3, 2014 Filing Review: November 15, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None Review: April 3, 2014 Filing Review: November 27, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Review: July 14, 2014 April 4, 2014 Filing Review: November 26, 2013
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☐ Not needed Review: February 24, 2014 Filing Review: November 15, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review dated 4/4/2014, page 52
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: May 28, 2014 June 26, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

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/s/

JUDIT R MILSTEIN

08/21/2014

NDA 206289-Action Package Checklist

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 30, 2014

Application Number: NDA 206289

Product Name: Atropine Sulfate Ophthalmic Solution, 1%

Sponsor/Applicant Name: Akorn, Inc.

Subject: Status of NDA 206289 action

FDA Participants:

Renata Albrecht, Director Division of Transplant and Ophthalmology Products

Wiley A. Chambers, Deputy Director

William M. Boyd, Clinical Team Leader

Judit Milstein, Chief Project Management Staff

Christina Marshall, Regulatory Health Project Manager

Sponsor/Applicant Participants:

Sam Boddapati, Senior Vice President, Regulatory Affairs

BACKGROUND:

NDA 206289 has a PDUFA goal date of April 30, 2014; however due to OAI findings at 2 of their manufacturing facilities before the application was submitted, and pending facility inspections, the PDUFA goal will not be met. The (b) (4) drug substance manufacturing site in (b) (4) was re-inspected in (b) (4) and the final evaluation by OMPQ is pending. The re-inspection of the Akorn, Decatur drug product manufacturing facility in follow up to a Warning Letter, is scheduled for May 2014, which is after the PDUFA goal date. The Office of Compliance stated the delay for the Akorn re-inspection is because they need to include a national expert for the inspection because of the violations at the Decatur facility.

DISCUSSION:

Dr. Albrecht informed Dr. Boddapati that the review of the application is currently ongoing, and since the Agency has not completed the review of the application, we will not be taking an Action on April 30, 2014. In response to Dr. Boddapati's question, Dr. Albrecht stated that Mrs. Marshall will provide a follow-up when there is an update on the status of the ongoing review.

ACTION ITEMS:

None

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/s/

CHRISTINA D MARSHALL

05/15/2014

NDA 206289-Tcon Memo



NDA 206289

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court, Suite #300
Lake Forest, IL 60045

Dear Dr. Boddapati:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by April 1, 2014, in order to continue our evaluation of your NDA.

1. Your response dated March 21, 2014, provided an update of the specifications in the relevant sub sections of 3.2.S.4.1 but was not updated in other sections. Update section 3.2.S.4.1 (Specification) with the current drug substance specifications from both (b) (4) and Akorn.
2. For the drug product specification, we have the following recommendations:
 - a. Our recommendation, as shown in the table below and communicated on March 14, 2014, remains unchanged. Your proposed acceptance criteria dated March 21, 2014 regarding the highest unknown impurity at NMT (b) (4) % is not acceptable as it is not aligned with ICH Q3B (R2). Therefore, revise the acceptance level of the highest unknown impurity to NMT (b) (4) %. We note that the level of NMT (b) (4) % is supported by available release and stability data for the 11 batches summarized in your response dated February 14, 2014. Any impurity above (b) (4) % (except (b) (4)) should be qualified and the result reported to the agency.

Parameter Description	NDA proposed	FDA proposed	NDA proposed	FDA proposed
	limit at release	limit at release	limit at stability	limit at stability

(b) (4)



- b. Revise 3.2.P.5.1 (Specification) to reflect NMT  in the 5 mL and 15 mL fill volumes.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
03/28/2014



NDA 206289

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court, Suite #300
Lake Forest, IL 60045

Dear Dr. Boddapati:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by March 21, 2014, in order to continue our evaluation of your NDA.

1. We have the following recommendations on the drug substance specification:

- a) We note that (b) (4), holder of DMF (b) (4), has updated the DMF with a new specification which reflects the current USP monograph. Please request (b) (4), for the new specification and update the NDA with the updated information.
- b) Revise to include (b) (4).
- c) The following tests are no longer described in the current USP monograph and you may opt to remove them from the specification: (b) (4).
- d) We note that you included (b) (4), respectively. The former one is described in the earlier version of USP monograph for atropine sulfate. The latter, associated with the (b) (4), can be removed from this specification.

2. The proposed acceptance criteria for (b) (4) are not aligned with ICH Q3B (R2), or not supported by the available batch release and stability data. Please revise the acceptance criteria as follows and revise the (b) (4) part of the specification accordingly.

Parameter Description	NDA proposed	FDA proposed	NDA proposed	FDA proposed
-----------------------	--------------	--------------	--------------	--------------

	limit at release	limit at release	limit at stability	limit at stability
(b) (4)				

3. Since the only submitted 6 months accelerated stability data (batch# 041392) failed the assay of (b) (4) at 3 month and 6 month time point, provide 6 months stability data at intermediate storage condition of (b) (4) % RH per ICH Q1A (R2) requirement.
4. Based on review of the submitted drug product stability data, we recommend an expiration date of 18 months.
5. We note that some stability data were perhaps randomly generated to provide data from different time points for different batches. For example, (b) (4)
(b) (4)
The parameters listed in the specification should be tested completely.
6. Update 3.2. P.5.1, 3.2.P.5.6, 3.2.P.8.1, 3.2.P.8.2 and 3.2.P.8.3 accordingly to include and reflect the current specifications of the drug product.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
03/14/2014



NDA 206289

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court, Suite #300
Lake Forest, IL 60045

Dear Dr. Boddapati:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by February 17, 2014, in order to continue our evaluation of your NDA.

CMC

1. For the drug product specification(3.2.P.5.1), we have the following recommendations:
 - a. Since the inclusion of the additional tests in your current drug product specification effective Oct. 10, 2013, has any drug product batch been analyzed or reanalyzed for the newly added impurities under the new drug product specification? Provide batch analysis data along with impurity profile for these batches for evaluating the appropriateness of the newly proposed specification (effective Oct. 10, 2013).
 - b. Include an identity test for EDTA. Include and justify EDTA assay range for stability. It is noted that the "Current Specifications" for Akorn Code 5058, 5154 and 5155 effective 10-10-2013 showed EDTA assay for stability study at (b) (4) %. Submit the revised stability specification and updated post-approval stability protocol.
 - c. Include a test for particulate matter to comply with USP <789>, table 2.
2. For the drug product stability (3.2.P.8), we have the following recommendations:
 - a. Your current accelerated testing conditions of 40° C ± 2° C/15% ± 5% RH is not aligned with ICH Q1A (R2) recommended storage condition (b) (4). Provide justification with data for use of the above referenced storage condition. Provide 6 months accelerated stability data and corresponding summary table following ICH Q1A (R2) conditions (40° C ± 2° C/ NMT 25% RH) for three registration batches for each of the three proposed configurations.
 - b. Provide stability data and corresponding summary table for all the batches stored under long-term storage conditions listed in 3.2.P.8.1.

- c. All long-term and accelerated stability data should be evaluated per the new proposed specification effective Oct. 10, 2013.
3. Provide droplet volume (drop size) evaluation data from multiple container batches.
4. On page 10-12 of section 3.2.P.5.4, the release test results provided is for three batches of the 15 mL configuration, but is shown as NLT (b) (4) for the recovery volume in the specification. Please verify and revise the NDA section accordingly.
5. In Section 3.2.P.1, the table (in the last page of this section) shows Akorn code for the 2 mL fill size to be 5054 but elsewhere in the NDA is referenced as 5058 - please clarify whether it is 5054 or 5058 and revise the NDA sections accordingly.
6. On page 1 of 3.2.P.3.2, you mention that the Akorn code for the 5 mL fill size as 5055 but mentioned elsewhere as 5154 - please clarify whether it is 5055 or 5154 and revise the NDA sections accordingly.

Microbiology

- (b) (4).
7. Confirm which facilities will be used (b) (4) for the drug product.
 8. (b) (4)
 9. Provide the most recent (b) (4) facilities.
 10. Confirm that all studies, original and recent, adequately validate the container and closure specified for the drug product. Note that the original (b) (4) identify components that are not identified in the subject submission.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
02/03/2014

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/s/

NAVDEEP BHANDARI
12/18/2013



NDA 206289

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court Suite 300
Lake Forest, IL 60045

Dear Dr. Boddapati:

Please refer to your New Drug Application (NDA) dated October 23, 2013, received October 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Atropine Sulfate Ophthalmic Solution 1%.

We also refer to your amendments dated October 29, and November 4, 2013.

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 is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is April 30, 2014.

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 April 9, 2014.

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.

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. 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 Christina Marshall, Regulatory Project Manager, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
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/

RENATA ALBRECHT
12/12/2013



NDA 206289

INFORMATION REQUEST

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court, Suite #300
Lake Forest, IL 60045

Dear Dr. Boddapati:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by December 10, 2013, in order to continue our evaluation of your NDA.

Although Akorn is not performing release testing for DS manufacturer, in 3.2.S.4.4, you did include API release data generated by Akorn and stated that "Prior to use in the manufacture of exhibit batches of drug product, drug substance is analyzed and released by Akorn, Inc. located at 1222 West Grand Avenue, Decatur, IL (FEI #1450114)"; therefore this Akorn Decatur IL site is considered as an API release testing facility and this function should be listed in 3.2.S.2.1.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
12/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206289

UNACCEPTABLE FOR FILING

Akorn, Inc.
Attention: Sam Boddapati, PhD
Senior Vice President, Regulatory Affairs
1925 West Field Court, Suite #300
Lake Forest, IL 60045

Dear Dr. Boddapati:

We have received your new drug application (NDA) submitted under section 505(b)/ pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Atropine Sulfate ophthalmic solution, USP 1%

Date of Application: October 22, 2013

Date of Receipt: October 30, 2013

Our Reference Number: NDA 206289

We note that your application, dated October 22, 2013, and received electronically on October 23, 2013, included the required Prescription Drug User Fee Cover Sheet (FDA Form 3397, User Fee I.D. Number #3013720); however, the appropriate user fee was not received at that time. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid (see section 736(e) of the Federal Food, Drug, and Cosmetic Act).

However, we also note that the appropriate user fee for this application was received by the Office of Financial Management on October 30, 2013. Consequently, we will consider October 30, 2013, as the receipt date for this application.

Please cite the NDA number listed above 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

If you have any questions regarding this application, contact me at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Christina Marshall, MS
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTINA D MARSHALL
11/06/2013
NDA 206289- UN/ACK letter



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118218

MEETING MINUTES

Akorn, Inc.
Attention: Sam Boddapati, Ph.D.
Senior Vice President, Regulatory Affairs
1925 West Field Court
Lake Forest, IL 60045

Dear Dr. Boddapati:

Please refer to your Pre-Investigational New Drug Application (PIND) file for atropine sulfate ophthalmic solution.

We also refer to the meeting between representatives of your firm and the FDA on May 21, 2013. The purpose of the meeting was to discuss the following:

1. The suitability of the 505(b)(2) pathway for approval of the proposed atropine sulfate ophthalmic solution, 1% product.
2. NDA submission based on literature-based nonclinical and/or clinical studies to support the NDA filing.
3. Any concerns that the Division may have with regard to other filing issues specific to the proposed product.
4. Guidance as to whether the Agency believes that the available information supporting the safety and efficacy of ingredients for the proposed product would satisfy the requirements for NDA approval.

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

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff at (301) 796-1600.

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Guidance
Meeting Date and Time: May 21, 2013 from 12:00 to 1:00 PM
Meeting Location: White Oak Building 22
Application Number: PIND 118218
Product Name: atropine sulfate ophthalmic solution
Indications: use in producing cycloplegia and mydriasis/ (b) (4)
(b) (4) for pupil dilation
Sponsor Name: Akorn, Inc.
Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Diana Willard

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Gerlie Gieser, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Yan Wang, Ph.D.	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Abel Eshete, Ph.D.	Statistical Reviewer, OB/DBIV
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Balajee Shanmugan, Ph.D.	Product Quality Reviewer, ONDQA/Branch V
Mark Seggel, Ph.D.	Biopharmaceutical Reviewer, ONDQA
Diana Willard	Chief, Project Management Staff, DTOP

AKORN, INC., ATTENDEES

Sam Boddapati, Ph.D.	Senior Vice President, Regulatory Affairs
Bruce Kutinsky, Pharm. D.	Chief Operating Officer

AKORN, INC. CONSULTANTS/THE FDA GROUP LLC

(b) (4)

BACKGROUND

A March 28, 2013, correspondence, received March 29, 2013, requested a meeting regarding PIND 118218 to discuss the following:

1. The suitability of the 505(b)(2) pathway for approval of the proposed atropine sulfate ophthalmic solution, 1% product.
2. NDA submission based on literature-based nonclinical and/or clinical studies to support the NDA filing.
3. Any concerns that the Division may have with regard to other filing issues specific to the proposed product.
4. Guidance as to whether the Agency believes that the available information supporting the safety and efficacy of ingredients for the proposed product would satisfy the requirements for NDA approval.

A Meeting Granted letter issued April 12, 2013, listing May 21, 2013, as the agreed upon meeting date.

The Meeting Package, dated April 22, 2013, was received on April 23, 2013. Agency responses to the questions in the April 22, 2013, Meeting Package were archived and sent, via e-mail to Akorn, Inc. (Akorn), on May 14, 2013.

DISCUSSION

The questions outlined in your April 22, 2013, Meeting Package are presented in **bold** font, our Meeting Preliminary Comments sent to Akorn May 14, 2013, are in *italic* font, and May 21, 2103, meeting discussion is in regular font.

Regulatory/Clinical

1. **Does the FDA concur that Akorn can file its New Drug Application (NDA) for Atropine Sulfate Ophthalmic Solution, 1%, under section 505(b)(2)?**

FDA Response: The 505(b)(2) pathway is acceptable provided you intend to support the NDA with studies that you did not conduct and to which you have no right of reference.

Meeting Discussion: None

2. Akorn plans to use the labeling for the approved products as the basis for updating the labeling for its proposed ophthalmic solution product. Does the Agency find this approach acceptable?

FDA Response: Potentially. Since the dosing regimen of the approved atropine sulfate products is different than your proposed product, some sections of the labeling for the approved products may be applicable while other sections may not.

Meeting Discussion: Akorn stated that they plan to use selected labeling sections of the two currently approved injectable atropine products for their planned NDA. The Agency stated that it is acceptable to use wording from approved labeling that applies to the product Akorn plans to submit as an NDA but noted that there are sections in the approved labeling that do not apply to Akorn's product.

Further, it was noted that Akorn should follow the format for submission of an NDA, and if there are sections that do not apply to their atropine application, Akorn can state this in the application, and explain why if the reason is not obvious.

3. Does the FDA concur with Akorn that the listed clinical efficacy studies in Table 3 and pharmacokinetic studies in Table 4 are sufficient to support the safety and efficacy of atropine sulfate ophthalmic solution, 1%, for the proposed indications?

FDA Response: Potentially. The clinical studies listed in Table 3 and the pharmacokinetic studies in Table 4 are potentially sufficient to support the filing of a 505(b)(2) NDA for the indications cycloplegia and mydriasis. The Division expects the studies in the literature that you plan to rely on to support your application to contain data that evaluates accommodation and pupil size. Approvability is a review issue requiring review of the entire NDA submission.

Meeting Discussion: The Division stated that Akorn should summarize how the literature studies submitted in any future NDA support the safety and efficacy of atropine sulfate ophthalmic solution, 1%, for use in the proposed indications using Akorn's proposed dosing regimen.

Responding to questions regarding

(b) (4)

If that were to be

the case, only one User Fee would be paid. [REDACTED] (b) (4)

The Division recommended that if Akorn had further questions [REDACTED] (b) (4)

[REDACTED] they contact Mike Jones in the Office of Regulatory Policy.

4. Akorn plans to confirm the dosing regimen for the ophthalmic solution from the efficacy studies summarized in Table 3. Is this approach acceptable?

FDA Response: It is acceptable to rely on the studies in the literature which utilize your proposed dosing regimen to support your planned 505(b)(2) application.

Meeting Discussion: None

5. Akorn is planning to rely on the published literature in pediatric patients to support the pediatric safety and efficacy. Does the FDA concur?

FDA Response: Concur that there is likely adequate information in the literature to support the indications cycloplegia and mydriasis in pediatric patients as well as adequate information to support [REDACTED] (b) (4) of atropine sulfate ophthalmic solution [REDACTED] (b) (4)

Meeting Discussion: The Division noted that if Akorn chose to submit an NDA for only the 1% atropine sulfate ophthalmic solution, they would need dosing information on all age groups. If Akorn felt that the [REDACTED] (b) (4) concentration was needed to support some of the age groups, they should plan on submitting both concentrations. If additional clinical trials are needed to support the [REDACTED] (b) (4) atropine sulfate ophthalmic solution in pediatric patients, a deferral of those trials could be requested.

6. Does the FDA agree that sufficient information is available from the literature to support the filing of Akorn's NDA and that no further pre-clinical or clinical studies are necessary?

FDA Response: We agree that there is likely adequate clinical information in the literature to support the filing of a 505(b)(2) application.

Please submit your selection criteria for the literature you plan to use to support the filing of the new drug application.

Please include literature to address female fertility and developmental toxicity.

Meeting Discussion: The sponsor stated that no information was available in the literature regarding female fertility or developmental toxicity. It was noted that the Division had

identified a number of articles regarding the effects of atropine on female reproductive tissues, teratogenesis, labor/delivery and lactation. Further, Akorn should provide an overall summary of all nonclinical data submitted. Each nonclinical element should be addressed and supported by cited literature.

The Division informed Akorn that they should always provide the search criteria used for preclinical and clinical literature submitted to an NDA.

- 7. As per 21 CFR 320.22 (b), Akorn intends to submit a waiver of the requirement to submit evidence of in vivo bioavailability or bioequivalence (BA/BE) for its Atropine Sulfate Ophthalmic Solution 1% product with the NDA application. Does the Agency agree that Atropine Sulfate Ophthalmic Solution is eligible for a BA/BE waiver?**

FDA Response: Agree. Since there is no approved NDA or ANDA for Atropine Sulfate Ophthalmic Solution 1%, the requirement to submit a waiver of in vivo BA/BE, as per 21 CFR 320.22(b), is not applicable. However, you do not need to conduct an additional clinical pharmacokinetic (PK) study to determine the systemic exposure to atropine and/or the pharmacologically active l-hyoscyamine following topical ocular administration of your proposed product since there appears to be adequate PK information from the literature, i.e., Table 4 of your PIND meeting package, that you plan to provide in your NDA submission.

Meeting Discussion: None

- 8. Does this NDA qualify for a Priority Review based on the unmet need for this drug product?**

FDA Response: A determination regarding the priority status of an application is only made after submission.

Meeting Discussion: The Division stated that Akorn can make a request for priority review in their cover letter, but they also need to provide reasoning, and documentation if appropriate, for the request.

Non-clinical Pharmacology and Toxicology

- 9. Akorn plans to rely on the labeling for the approved reference product and the literature summarized in Table 2 above for the pre-clinical pharmacology and toxicology sections of its NDA. Does the FDA agree with this plan?**

FDA Response: Yes.

Meeting Discussion: None

Additional Agency Comments:

In the NDA, provide an integrated summary of the nonclinical data/literature being relied upon to support the application and include copies of all cited publications. Published literature is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. Provide discussion of the potential impact of study shortcomings (e.g., insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.

Additional Meeting Discussion: The Agency recommended that the sponsor schedule a pre-NDA CMC meeting to discuss issues such as the stability requirements for the proposed atropine sulfate ophthalmic solutions.

ACTION ITEMS: The Division will issue meeting minutes in 30 days.

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/s/

WILEY A CHAMBERS
06/06/2013