

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208254Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208254 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Rhopressa Established/Proper Name: netarsudil Dosage Form: ophthalmic solution, 0.02%		Applicant: Aerie Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Eithu Lwin		Division: Division of Transplant and Ophthalmology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)               <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check: <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is February 28, 2018</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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): Type 1  
 (confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(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

- 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: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Social Media (Twitter)
❖ 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) ( <a href="#">link</a> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees ( <a href="#">link</a> )	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval 12/18/2017
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 12/12/2017
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 02/28/2017
❖ 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>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 12/12/2017
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	Acceptable 05/18/2017
• Review(s) <i>(indicate date(s))</i>	Review 05/16/2017 & 10/21/2016
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 06/19/2017 DMEPA: 07/13/2017 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 11/15/2017 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	06/19/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>10/25/2017</u></li> <li>If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> <li>❖ 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.) (<i>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</i>)</li> </ul>	Information Requests: 10/30/2017, 10/21/2017, 07/20/2017, 07/20/2017, 07/17/2017, 06/16/2017, 05/15/2017, 05/10/2017, 04/04/2017, 04/04/2017, 10/06/2016, 10/04/2016
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	10/27/2015
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	04/11/2014
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	07/25/2017
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	09/29/2017
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	Pre-NDA CMC 12/17/2015 EOP2 CMC 03/10/2014
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	10/13/2017
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	Combined with CDTL Review
<ul style="list-style-type: none"> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	Combined with CDTL Review
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	12/15/2017
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input checked="" type="checkbox"/> None

<b>Clinical</b>	
❖ <b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	11/08/2017, Filing 04/10/2017 and 10/11/2016
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	Located on page 100 of the 11/08/2017 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) <sup>5</sup>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</li> <li>• REMS Memo(s) and letter(s) (indicate date(s))</li> <li>• 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)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	Inspection Summary 09/24/2017 Letter to applicant: 10/10/2017 Letter to investigators: 10/13/2017, 08/29/2017
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	12/11/2017 Filing 04/11/2017 and 10/18/2016
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	08/30/2017, Filing 10/7/2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

<sup>5</sup> 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).

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	11/06/2017, Filing 03/31/2017 and 10/03/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review (indicate date for each review)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	10/30/2017 Filing 04/03/2017 and 10/28/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Located on page 93 of the IQA 10/30/2017
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	Located on page 163 of the IQA 10/30/2017 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

<b>Day of Approval Activities</b>	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications:                             <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ For Breakthrough Therapy (BT) Designated drugs:                             <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul> </li> </ul>	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> <li>❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> </li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure Pediatric Record is accurate</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send approval email within one business day to CDER-APPROVALS</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Take Action Package (if in paper) down to Document Room for scanning within <b>two business days</b></li> </ul>	

**PeRC Meeting Minutes**  
**October 25, 2017**

**PeRC Members Attending:**

Lynne Yao  
Jackie Yancy  
Gettie Audain  
Gerri Baer  
Dionna Greene  
Shrikant Pagay  
Susan McCune  
Lily Mulugeta  
Wiley Chambers  
Greg Reaman  
Raquel Tapia  
Dionna Greene  
Hari Cheryl Sachs  
Daiva Shetty  
Donna Snyder  
Barbara Buch  
Victor Baum  
James Travis  
Shrikant Pagay  
Maura O'leary  
Darren Fegley

**Agenda**

NON-RESPONSIVE

9:00	NON-RESPONSIVE
9:10	
9:20	
9:40	
9:50	
10:10	
10:30	
10:40	
10:50	
11:10	
11:30	
11:40	
12:00	

12:00	NON-RESPONSIVE				
	NON-RESPONSIVE				
	NDA 208254	Rhopressa (netarsudil) Ophthalmic solution Full Waiver (with an Agreed iPSP)	DTOP	Ei Thu Lwin	For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
	NON-RESPONSIVE				

11 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

**Rhopressa (netarsudil) Ophthalmic Solution Full Waiver (with an Agreed iPSP)**

- Proposed indication: For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
- *PeRC Recommendations:*

- The PeRC agrees with the division to grant this full waiver as agreed upon in the iPSP.

NON-RESPONSIVE

NON-RESPONSIVE

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

/s/  
-----

MESHAUN L PAYNE  
11/20/2017



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

---

**DATE:** October 30, 2017

<b>To:</b> Cindy Martin Vice President, Regulatory	<b>From:</b> Eithu Z. Lwin, PharmD Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Find enclosed information request for NDA 208254

---

**Total no. of pages including cover:** 3

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Aerie Pharmaceuticals, Inc.  
Attention: Ms. Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following request for additional information.

**Clinical**

1. In your briefing document on page 65 you provide pooled safety from 4 trials (301, 302, 303, and 304). Please provide a table similar to this table with pooled safety analysis for the following 3 trials: Studies 301, 302, and 304 (excluding data from study 303).

We request a response by November 3, 2017. Please let me know if you need additional time.

If you have any questions regarding this request, please contact me at 301-796-0728.

Sincerely,

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
10/30/2017  
NDA 208254, Clinical IR



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

---

**DATE:** October 21, 2017

<b>To:</b> Cindy Martin Vice President, Regulatory	<b>From:</b> Eithu Z. Lwin, PharmD Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Find enclosed information request for NDA 208254

---

**Total no. of pages including cover:** 2

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Aerie Pharmaceuticals, Inc.  
Attention: Ms. Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following requests for additional information.

**Clinical**

1. Please state the location for the financial disclosure for Study 304.
2. Please provide tables for all treatment emergent AEs for pooled population for Studies 301, 302, and 304. Please submit updated label with this pooled safety information.

We request a response by October 27, 2017. Please let me know if you need additional time.

If you have any questions regarding this request, please contact me at 301-796-0728.

Sincerely,

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
10/21/2017  
NDA 208254 Clinical IR



NDA 208254

**MID-CYCLE COMMUNICATION**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Vice President, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa (netarsudil ophthalmic solution) 0.02%.

We also refer to the teleconference between representatives of your firm and the FDA on July 25, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Eithu Lwin, Regulatory Project Manager at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

William M. Boyd, MD  
Cross Discipline Team Leader  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** July 25, 2017, from 3:15 PM – 4:00 PM (EST)

**Application Number:** NDA 208254  
**Product Name:** Rhopressa (netarsudil ophthalmic solution) 0.02%  
**Indication:** reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension  
**Applicant Name:** Aerie Pharmaceuticals, Inc.

**Meeting Chair:** William Boyd, Cross Discipline Team Leader (CDTL)  
**Meeting Recorder:** Eithu Lwin, Regulatory Health Project Manager

**FDA ATTENDEES**

John Farley, Deputy Director, Office of Antimicrobial Products  
Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)  
William M. Boyd, Cross Discipline Team Leader (CDTL), DTOP  
Jane Filie, Associate Director for Labeling, DTOP  
Lucious Lim, Clinical Reviewer, DTOP  
Rhea Lloyd, Clinical Reviewer, DTOP  
Martin Nevitt, Clinical Reviewer, DTOP  
Maria Rivera, Pharmacology/Toxicology Reviewer, DTOP  
Aling Dong, Pharmacology/Toxicology Reviewer, DTOP  
Yunfan Deng, Statistics Reviewer, DTOP  
Philip Colangelo, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV  
Yushi Feng, Product Quality Team Leader, Office of New Drug Product  
LaToya Bonner, Designated Federal Officer, Dermatology and Ophthalmology Drug Advisory Committee  
Roy Blay, Reviewer, Office of Scientific Integrity  
Abiola Olagundoye, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)  
Yasmeen Abou-Sayed, Risk Management Analyst, Division of Risk Management  
Mingfeng Zhang, Epidemiology Reviewer, Division of Epidemiology  
Madhuri Patel, Safety Evaluator, Division of Medication Error Prevention and Analysis  
Derek Alberding, Regulatory Health Project Manager, DTOP  
Eithu Z. Lwin, Regulatory Health Project Manager, DTOP

**APPLICANT ATTENDEES**

Tom Mitro, President and Chief Operating Officer  
Theresa Heah, Vice President, Clinical Research and Medical Affairs

Mid-Cycle Communication

Casey Kopczynski, Chief Scientific Officer  
Marvin Garrett, Vice President, Regulatory Affairs and Quality  
Cindy Martin, Vice President, Regulatory Affairs  
Kristine Erickson, Vice President, Clinical Research  
Ken Ruettimann, Vice President, Manufacturing  
George Baklayan, Director, Regulatory Affairs/Technical Writing

(b) (4)

## DISCUSSION

For the purposes of these minutes, the information that the CDTL presented are in normal font and the meeting discussions are in *italics*.

### 1. INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

You are reminded that the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211.

*Discussion: None*

### 2. SIGNIFICANT ISSUES

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.

*Discussion: Applicant inquired how this issue would impact the application. The Division responded that it could have labeling ramifications.*

*Applicant inquired if the final clinical study report for AR-13324- CS304 submitted on June 23, 2017, will be reviewed. The Division responded that it may or may not be reviewed in this cycle as time permits.*

- Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.

*Discussion: Applicant inquired if the Division considers cornea verticillata and corneal opacities to be the same entity or different entities. Applicant stated that based on the new MEDRA coding, their events were all coded as cornea verticillata. The Division*

Mid-Cycle Communication

*responded that they are still reviewing the submitted data to understand the impact, duration, and the cause of the corneal changes. The Division noted that these corneal changes do not occur with other ophthalmic intraocular pressure lowering agents.*

### **3. INFORMATION REQUESTS**

To date, there is one CMC Information Request that was issued on July 20, 2017, that is pending response.

*Discussion:* Applicant agreed to have their responses formally submitted by August 4, 2017.

### **4. MAJOR LABELING ISSUES**

Aerie submitted revised labeling on May 11, 2017. As stated in the Filing Letter, if major deficiencies are not identified during the review, we plan to communicate proposed labeling by November 24, 2017.

*Discussion:* None

### **5. REVIEW PLANS**

- There are no Risk Evaluation & Mitigation Strategies (REMS) identified to date for this application beyond routine draft professional labeling for the product. Potential risk management actions will be discussed at the Advisory Committee (AC) Meeting on Friday, October 13, 2017.

*Discussion:* The Applicant inquired if draft questions will be available ahead of time before the AC meeting. The Division responded that it anticipates that the draft discussion issues will be provided approximately one month before the AC meeting.

*The Applicant also inquired when the Federal Register (FR) notice of the AC meeting will be posted. The Division responded that the last day for posting the FR notice is 15 days before the meeting.*

- The PDUFA goal date for this application is February 28, 2018 (Standard NME).

*Discussion:* None

### **6. WRAP-UP AND ACTION ITEMS**

- Late-Cycle Meeting is currently scheduled for September 29, 2017, 10:00 AM to 11:00AM (EST).
- The meeting minutes for this Mid-Cycle Communication will be issued within 30 days.

*Discussion:* None

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

/s/  
-----

WILLIAM M BOYD  
08/08/2017



NDA 208254

**INFORMATION REQUEST**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 100  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated and received February 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa™, netarsudil ophthalmic solution, 0.02%.

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

Drug Substance:

1. Based on the Residue on Ignition test results of batches produced by the proposed commercial route, tighten acceptance criterion limit to (b) (4) %. We acknowledge that you are proposing to (b) (4)

Microbiology:

2. Regarding your response to the Agency's 6/16/2017 deficiency #4a, please note that the request is for (b) (4) studies as already provided in the submission. The Agency acknowledged that report 123-P-17 and 123-P-18 for (b) (4) and 344-P-13, 344-D-02 for (b) (4) are provided in the submission. However, these reports only contain (b) (4) studies. Please provide validation data for (b) (4) studies to demonstrate (b) (4) and clarify whether these studies were performed (b) (4)
3. Regarding your response of 07/10/2017 to the 06/16/2017 deficiency #10(a), it is noted that the (b) (4) and (b) (4)

(b) (4) However, the validation data as provided in Report #011-P-21 for the (b) (4) studies performed in 2016, 2014, and 2012 showed (b) (4) respectively. Please justify how the 2016 and 2014 studies met your acceptance criteria of (b) (4). Please provide the most recent validation study that demonstrates the (b) (4)

4. Regarding your response to deficiency 10(b): Per your response, (b) (4)

(b) (4)

If you have any questions, please contact me at (240) 402-5834. Please respond to these comments by **COB August 4, 2017**.

Sincerely,  
**Kristine F.  
Leahy -S**

Digitally signed by Kristine F. Leahy -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2001815977,  
cn=Kristine F. Leahy -S  
Date: 2017.07.20 20:37:14 -0400

Kristine Leahy, RPh.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

---

**DATE: July 20, 2017**

<b>To: Cindy Martin Vice President, Regulatory</b>	<b>From: Eithu Z. Lwin, PharmD Regulatory Project Manager</b>
<b>Company: Aerie Pharmaceuticals, Inc.</b>	<b>Division of Transplant and Ophthalmology Products</b>
<b>E-mail: cmartin@aeriepharma.com</b>	<b>E-mail: Eithu.Lwin@fda.hhs.gov</b>
<b>Phone Number: 949-526-8698</b>	<b>Phone Number: 301-796-0728</b>

**Subject: Find enclosed information request for NDA 208254**

---

**Total no. of pages including cover: 3**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS  
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND  
PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Aerie Pharmaceuticals, Inc.  
Attention: Ms. Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following request for additional information.

**Clinical**

In the Safety Update submitted 6/23/17, the literature references cited on page 35 and 36 of Clinical Study Report: AR-13324-OBS01 [A prospective, targeted, non-interventional (observational) study of subjects who developed corneal deposits in clinical trials AR-13324-CS301 and AR-13324-CS302] were not provided.

Please submit the cited references to the NDA in their entirety. If these references have been previously submitted to the NDA, please provide their exact location.

We request a response by August 2, 2017.

If you have any questions regarding this request, please contact me at 301-796-0728.

Sincerely,

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
07/20/2017  
NDA 208254



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

---

**DATE:** July 17, 2017

<b>To:</b> Cindy Martin Vice President, Regulatory	<b>From:</b> Eithu Z. Lwin, PharmD Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Find enclosed information requests for NDA 208254

---

**Total no. of pages including cover:** 3

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Aerie Pharmaceuticals, Inc.  
Attention: Ms. Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following requests for additional information.

**Clinical**

1. Regarding Study AR-13324-CS302 please provide narratives for all serious treatment emergent AEs regardless of whether patient was discontinued or not. If these have been submitted previously please provide the exact location.
2. Regarding Study AR-13324-CS302 please provide a table which presents the treatment emergent adverse events for  $\geq 1\%$  for the safety population.

We request that you provide a response by July 31, 2017.

If you have any questions regarding this request, please contact me at 301-796-0728.

Sincerely,

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
07/17/2017  
NDA 208254



NDA 208254

**INFORMATION REQUEST**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 100  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated and received February 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa™, netarsudil mesylate ophthalmic solution, 0.02%.

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

Drug Product:

1. We note that in P.8.1, pages 11 and 12 you state: "As requested by the agency Quality Reviewer per the email sent October 6, 2016, one registration stability lot following storage for 24 months at  $5 \pm 3^{\circ}\text{C}$  was placed on stability for an additional six weeks at  $25 \pm 2^{\circ}\text{C}/40 \pm 5\%$  RH to support the in-use storage condition. The results from this study (Protocol P-00004) will be submitted during the review period." Please provide a tentative date for the submission of this report.

Microbiology:

1. Regarding WFI monitoring, please describe the WFI storage conditions, frequency of testing and the user points tested, and confirm if WFI is tested for bioburden and bacterial endotoxins on a per batch basis.

2. Regarding [REDACTED]

(b) (4)

(b) (4)

3 Pages have been Withheld in Full as b4  
(CCI/TS) immediately following this page

If you have any questions, please contact me at (240) 402-5834 or email:  
[kristine.leahy@fda.hhs.gov](mailto:kristine.leahy@fda.hhs.gov). Please respond to these comments by **COB July 10, 2017**.

Sincerely,  
**Kristine F.  
Leahy -S**

Digitally signed by Kristine F. Leahy -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=20018159  
77, cn=Kristine F. Leahy -S  
Date: 2017.06.16 16:57:33 -0400

**Kristine Leahy, RPh.**  
**Regulatory Business Process Manager**  
**Office of Program and Regulatory Operations**  
**Office of Pharmaceutical Quality**  
**Center for Drug Evaluation and Research**



NDA 208254

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Aerie Pharmaceuticals, Inc.  
2030 Main St., Suite 1500  
Irvine, CA 92614

ATTENTION: Cindy Martin  
Vice President, Regulatory

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated and received February 28, 2017, resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Netarsudil Ophthalmic Solution, 0.02%.

We also refer to your correspondence, dated and received February 28, 2017, requesting review of your proposed proprietary name, Rhopressa.

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

If any of the proposed product characteristics as stated in your February 28, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Abiola M. Olagundoye-Alawode, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3982. For any other information regarding this application, contact Ei Thu Lwin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0728.

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

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

/s/  
-----

DANIELLE M HARRIS on behalf of TODD D BRIDGES  
05/18/2017



NDA 208254

## INFORMATION REQUEST

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 100  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated and received February 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa™, netarsudil mesylate, ophthalmic solution, 0.02%.

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

### Environmental Assessment:

- The applicant did not submit a correct and complete claim of categorical exclusion as required at 21 CFR 25.15 (a) and (d). Based on the provided manufacturing information, the proper exclusion for this application is cited at 21 CFR 25.31(b). The exclusion that was provided (21 CFR 25.31(a)) is for the type of applications listed on page 29 of CDER's EA Guidance\*. In addition, an explicit statement that 'no extraordinary circumstances' exist was not submitted. The required statement concerning extraordinary circumstances is discussed at 21 CFR 25.21. Please submit a corrected claim of categorical exclusion.*

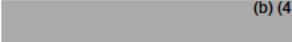
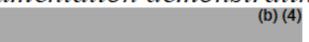
\*CDER EA Guidance:

<https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf>

### Drug Product:

- Provide a listing of files in Section 3.2 of the Amendment of 2/28/17 that have been changed with respect to the versions submitted in the original NDA of 8/30/16 and the Amendments of 10/13/16 and 10/17/16. For each file that has been changed please briefly indicate the nature of the change.*

Drug Process:

3. (b) (4)  
  
*Such parameters should be supported by development data and/or registration batch manufacturing data. Revise the pertinent section of P.3 accordingly.*
4. Provide a  (b) (4) *in compliance with 21 CFR 211.115 and include it in 3.2.P.3.3.*
5. *Provide supporting data to justify the proposed maximum permissible bulk hold time specified for each manufacturing step. In addition, we recommend that such bulk hold time be included in the intended commercial batch records.*
6. *Provide compatibility data  (b) (4) to be used for the intended commercial batches.*
7. *Provide documentation demonstrating compliance of all polymeric formulation contact components  (b) (4) intended for use during commercial manufacturing with pertinent CFR regulations for indirect food additive as well as USP <87> and <88>. In addition, provide a statement for the  (b) (4) components  (b) (4)  (b) (4) to meet the ASTM or equivalent standards for  (b) (4)*
8. *Provide reconciliation tables for all registration batches including theoretical yield, maximum and minimum percentages of theoretical yield, and actual yield determined at the conclusion of each appropriate phase of manufacturing, processing, packaging or holding of the drug product, wherever is applicable. Provide justification for any significant waste and/or rejections and batch-to-batch variability.*

If you have any questions, please contact me at (240) 402-5834 or email: [kristine.leahy@fda.hhs.gov](mailto:kristine.leahy@fda.hhs.gov).  
Please respond to these comments by **COB June 9, 2017**.

Sincerely,  
**Kristine F.  
Leahy -S**

 Digitally signed by Kristine F. Leahy -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2001815977,  
cn=Kristine F. Leahy -S  
Date: 2017.05.15 16:08:48 -04'00'

Kristine Leahy, RPh.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



NDA 208254

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

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated and received on February 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Rhopressa (netarsudil ophthalmic solution) 0.02%.

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 **Standard**. Therefore, the user fee goal date is February 28, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

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 commitment requests by November 24, 2017.

In addition, the planned date for our internal mid-cycle review meeting is July 17, 2017. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. 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.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. The checklist is available at the following link:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>

## **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 acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Eithu Z. Lwin, Regulatory Project Manager, at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, MD  
Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

RENATA ALBRECHT  
05/11/2017



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

---

---

**COMMUNICATION SHEET**

---

---

**DATE:** May 10, 2017

<b>To: Cindy Martin</b> Vice President, Regulatory	<b>From: Eithu Z. Lwin, PharmD</b> Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Labeling formatting recommendations for NDA 208254

---

**Total no. of pages including cover:** 7

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Aerie Pharmaceuticals, Inc.  
Attention: Ms. Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. As submitted, your label is not in compliance with the labeling formatting requirements as described in 21 CFR 201.56 and 201.57. Please see the attached labeling with our recommendations.

The following are resources to assist you in formatting your labeling:

- Sample Template –Highlights, Contents, and Full Prescribing Information at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM340915.docx>
- Selected Requirements of Prescribing Information (SRPI): The SRPI is a checklist review of 41 important format items from labeling regulations and guidances at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>
- Guidance for industry “Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements”, particularly Appendix E Highlights and Contents Format Sample at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf>

We request that you resubmit revised labeling (in Microsoft Word format) that addresses these issues by May 31, 2017, so a substantive review of the labeling can be initiated.

If you have any questions regarding this request, please contact me at 301-796-0728.

Sincerely,

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

EI THU Z LWIN  
05/10/2017  
NDA 208254  
Labeling Formatting Comments



NDA 208254

**NDA ACKNOWLEDGMENT  
RESUBMISSION AFTER WITHDRAWAL**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

We acknowledge your resubmission to your New Drug Application (NDA), dated and received on February 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa (netarsudil ophthalmic solution) 0.02%. We note that this NDA was originally submitted on August 29, 2016, and withdrawn on October 27, 2016.

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 29, 2017, in accordance with 21 CFR 314.101(a).

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 is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

Eithu Z. Lwin, PharmD  
Regulatory Health Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
04/07/2017  
NDA 208254



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

**DATE:** April 4, 2017

<b>To: Cindy Martin</b> Vice President, Regulatory	<b>From: Eithu Z. Lwin, PharmD</b> Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Find enclosed information request for NDA 208254

**Total no. of pages including cover:** 3

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Sponsor: Aerie Pharmaceuticals, Inc.  
Attn: Ms. Cindy Martin

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following request for additional information.

Please forward the following background information (1 CD per site) for the indicated sites to facilitate the OSI inspection process:

Investigators/Sites: David L. Cooke, M.D./Site #125  
Andrew G. Logan, M.D./Site # 251

Protocols: Dr. Cooke, AR-13324-CS301  
Dr. Logan, AR-13324-CS302

Data/Information Listings (background information):

- 1) Form 1572s for investigators and sub-investigators
- 2) Protocols and relevant amendments
- 3) Tabular data listings of subjects at each site, broken out to include:
  - a) Total number of subjects entered and completed per study arm
  - b) Drop-outs, with specific description/narrative
  - c) Indication of evaluable/non-evaluable subjects (yes/no response)
  - d) Protocol violations with specific description/narrative
  - e) Primary efficacy data listings per subject (and per site)
  - f) Adverse Events
  - g) Serious adverse events (with narratives)
  - h) Concomitant medications
  - i) Laboratory abnormalities
- 4) Randomization lists
- 5) Names and addresses of IRBs
- 6) A completed CRF for one subject at each site
- 7) Names/addresses of monitors and monitoring logs (attendance logs)
- 8) Beginning and end dates for the trials

Please submit this information by COB April 13, 2017.

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

/s/  
-----

EI THU Z LWIN  
04/04/2017  
NDA 208254 IR



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**COMMUNICATION SHEET**

**DATE:** April 4, 2017

<b>To:</b> Cindy Martin Vice President, Regulatory	<b>From:</b> Eithu Z. Lwin, PharmD Regulatory Project Manager
<b>Company:</b> Aerie Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
<b>E-mail:</b> cmartin@aeriepharma.com	<b>E-mail:</b> Eithu.Lwin@fda.hhs.gov
<b>Phone Number:</b> 949-526-8698	<b>Phone Number:</b> 301-796-0728

**Subject:** Find enclosed information request for NDA 208254

**Total no. of pages including cover:** 3

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.**

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

NDA 208254  
Rhopressa (netarsudil ophthalmic solution) 0.02%  
Sponsor: Aerie Pharmaceuticals, Inc.  
Attn: Ms. Cindy Martin

Dear Ms. Martin,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We have the following request for additional information.

**Statistical Information Request**

This NDA resubmission included a 3-month interim clinical study report for an on-going Phase 3 study (AR-13324-CS304). However, we cannot locate the raw and derived analysis datasets and SAS programs used to generate the efficacy and safety results presented in the interim study report. Please submit these datasets and program codes along with their define documents to us if they are not included in the resubmission or clarify where they are located in the resubmission.

Please provide a response by April 7, 2017.

If you have any questions regarding the contents of this transmission, please contact me at 301-796-0728.

Eithu Z. Lwin, PharmD  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/  
-----

EI THU Z LWIN  
04/04/2017  
NDA 208254 Rhopressa



NDA 208254

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

Aerie Pharmaceuticals, Inc.  
2030 Main St., Suite 1500  
Irvine, CA 92614

ATTENTION: Cindy Martin  
Vice President, Regulatory

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated February 28, 2017, received February 28, 2017, resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Netarsudil Ophthalmic Solution, 0.02%.

We acknowledge receipt of your correspondence, dated and received February 28, 2017, requesting a review of your proposed proprietary name, Rhopressa.

The goal date for your proposed proprietary name is May 29, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Ei Thu Lwin, Project Manager in the Office of New Drugs at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

Abiola M. Olagundoye-Alawode, PharmD, MS  
LCDR, USPHS  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

/s/

-----  
ABIOLA M OLAGUNDOYE-ALAWODE  
03/14/2017

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 26, 2016  
**TIME:** 12:00-13:30 PM  
**MEETING FORMAT:** Teleconference  
**APPLICATION:** NDA 208254  
**DRUG NAME:** Rhopressa (netarsudil ophthalmic solution). 0.02%

**MEETING CHAIR:** Wiley A. Chambers, Deputy Director

**MEETING RECORDER:** Judit Milstein, Chief, Project Management Staff

### FDA ATTENDEES:

Renata Albrecht, Director, Division of Transplant and Ophthalmology Products (DTOP)  
Wiley A. Chambers, Deputy Director, DTOP  
William M. Boyd, Clinical Team Leader, DTOP  
Sonal Wadhwa, Clinical Reviewer, DTOP  
Michael Puglisi, Regulatory Project Manager, DTOP  
Eithu Lwin, Regulatory Project Manager, DTOP  
Judit Milstein, Chief, Project Management Staff, DTOP  
Katherine Schumann, Associate Director for Regulatory Affairs, Office of Antimicrobial Products  
Chunchun Zhang, Acting CMC Lead, Office of Pharmaceutical Quality (OPQ)  
Derek Smith, Acting Branch Chief, Office of Process and Facilities (OPF), OPQ  
Denise DiGiulio, Facility Reviewer, Office of Process and Facilities (OPF), OPQ

### EXTERNAL CONSTITUENT ATTENDEES:

Tom Mitro, President and COO, Aerie Pharmaceuticals  
Marvin Garrett, VP RA and QA, Aerie Pharmaceuticals  
Cindy Martin, Director RA, Aerie Pharmaceuticals  
Ted Wheeler, Director QA, Aerie Pharmaceuticals

### BACKGROUND:

NDA 208254 was submitted on August 30, 2016, with a filing date of October 29, 2016. As the Agency is aware of issues related to the [REDACTED] <sup>(b) (4)</sup> drug manufacturing site, which is the same as Aerie intends to use for their product, an e-mail was sent to the applicant on October 4, 2016, requesting clarification on the inspection readiness for the drug product as follows:

With regard to your NDA 208254, please contact your proposed drug product manufacturer to confirm that the manufacturing lines proposed in your submission are currently ready for inspection. If the lines are not ready for inspection, please provide dates for when the lines will be ready.

The applicant responded on October 13, 2016, stating that:

The (b) (4) Certification of GMP Compliance dated 23 August 2016 included in the Rhopressa NDA states the (b) (4) facility complies with cGMP's in the procedures, facilities and controls used in the manufacture, process, packaging, labeling and testing of drug products. The (b) (4) facility was issued an NAI (No Action Indicated) rating for the FDA inspection conducted in (b) (4) per FDA's Inspections Classification Database (b) (4) is currently manufacturing and distributing commercial product on (b) (4) which is used to produce the Rhopressa™ (netarsudil ophthalmic solution) 0.02% drug product.

Aerie conducted an audit of the (b) (4) facility in early (b) (4) and the results were reviewed by ex-FDA consultants. It is Aerie's opinion that the (b) (4) is ready for the PAI (Pre-Approval Inspection). We have not observed any issues with our product manufactured on (b) (4). We are aware, however, that there were observations cited during the (b) (4) PAI audit regarding their NDA for (b) (4) and will be ready for re-inspection of (b) (4) by the end (b) (4).

Based on the ambiguity of this information, the Agency requested a teleconference with the applicant to confirm if the (b) (4) site is ready for inspection or not, as this information might determine the fileability of the application.

#### **MEETING OBJECTIVES:**

To obtain information from the applicant as to whether the (b) (4) facility is ready or not for inspection

#### **DISCUSSION POINTS:**

The applicant indicated that they have acted with due diligence before the application was submitted to confirm that in their opinion that the sites were ready for inspection, and that they feel that at this time, the (b) (4) facility is GMP compliant and ready.

The Division asked the applicant to confirm either if the (b) (4) site was or was not ready for inspection as this information might determine the fileability of the application. The Division further explained that if the application stands as is (facilities are ready as per FDA form 356h submitted with the original application), an inspection could occur before (b) (4). In such case, if the facility is not ready, it will be unlikely that the application would be approved in the current cycle as a second inspection may not be scheduled.

The Division further stated that if the (b) (4) facility is not ready for inspection, it is unlikely that the application will be filed. The Division further stated that if a Refuse to File was issued, the

applicant has the option of Filing over protest. The Division also indicated that another option would be for the applicant to withdraw the application.

The applicant inquired as to what information needs to be submitted to the application stating the readiness of the facility. The Division stated that if the facility is ready, the applicant should send a letter confirming the readiness. If the facility is not ready, the applicant will need to submit a revised FDA Form 356 h and corresponding cover letter. In the interest of time, the information should be emailed to Eithu Lwin and Judit Milstein, and then formally submitted to the application.

The Division concluded that generally if the FDA Form 356h form states the facility is ready for inspection, the expectation is the application would be filed, and if the FDA Form 356h (revised) says the facility is not ready for inspection, the expectation is that the application would not be filed.

The applicant stated that a confirmation on the readiness of the facility would be provided by COB, October 26, 2016.

**POST MEETING NOTES:**

On October 26, 2016, the applicant sent an e-mail to the Division stating that as they are a publicly traded company they needed to discuss this information with the Board of Directors prior to sending the information to the application, and that the response will be provided via e-mail no later than the morning of October 28, 2016, followed by a formal submission to the NDA.

On October 27, 2016, Aerie withdrew their NDA. Aerie stated in their submission:

*In accordance with 505(b)(1) of the Food, Drug and Cosmetic Act and 21 CFR 314.65 Aerie Pharmaceuticals, Inc. (Aerie) hereby withdraws, without prejudice to refiling, the original New Drug Application (NDA) for Rhopressa™ (netarsudil ophthalmic solution) 0.02%, a Rho kinase (b) (4) inhibitor developed at Aerie.*

**DECISIONS (AGREEMENTS) REACHED:**

None

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

None

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

/s/  
-----

EI THU Z LWIN

11/09/2016

NDA 208254 internal meeting memo



NDA 208254

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

Aerie Pharmaceuticals, Inc.  
2030 Main St., Suite 1500  
Irvine, CA 92614

ATTENTION: Cindy Martin  
Director Regulatory Affairs

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated August 30, 2016, received August 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Netarsudil Ophthalmic Solution, 0.02%.

We acknowledge receipt of your August 30, 2016, correspondence, received August 30, 2016, requesting a review of your proposed proprietary name, Rhopressa.

If the application is filed, the user fee goal date will be November 28, 2016.

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 Judit Milstein, Chief, Project Manager, in the Office of New Drugs at (301) 796-0763.

Sincerely,

*{See appended electronic signature page}*

Janet G. Higgins  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

/s/  
-----

JANET G HIGGINS  
10/07/2016

## Puglisi, Michael

---

**From:** Puglisi, Michael  
**Sent:** Thursday, October 06, 2016 9:23 AM  
**To:** Cindy Martin (cmartin@aeriepharma.com); Garrett Mr□ Marvin (Mgarrett@aeriepharma.com)  
**Cc:** Milstein, Judit; Lwin, Ei Thu  
**Subject:** Product Quality Information Request for Rhopressa - NDA 208254

Hi Cindy and Marv,

Below please find comments from our Quality Reviewer for the Rhopressa (netarsudil ophthalmic solution) NDA, which was submitted on August 30, 2016. I'm sending these comments on behalf of my colleague, Eithu Lwin.

Please confirm receipt and let us know if you have any questions about the comments. The reviewer has requested a response within four weeks, if possible. 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

### Product Quality Reviewer's Comments:

- We remind you that if the cap color changes the change should be submitted as a Prior Approval Supplement including the results of extractables testing and a commitment to carry out leachables testing (IND 113064, minutes of the December 17, 2015 meeting, dated 1/14/16, see Question 10).*
- Please provide sample Certificates of Analysis showing that the water for injection meets all aspects of the USP standards.*
- With regard to the HPLC method for benzalkonium chloride we note that robustness is not demonstrated. WE note in Report MVR-1945, page 10 of 39, that the (b) (4)*  
*Please provide a robustness report or a justification for not conducting robustness testing.*
- In Report M-030-13 particulate matter is tested by (b) (4)*  
*(b) (4)*

5. *In the drug product specification please [REDACTED] (b) (4) or provide a justification for not doing so.*
6. *We note that the [REDACTED] (b) (4) Please comment.*
7. *We note your statement that after opening, the product may be kept at 2°-25°C for up to 6 weeks. Please support this statement by conducting a one-time stability test for one batch of each presentation stored at 2-8°C for 24 months then at 25°C/40% RH for 6 weeks.*

-----  
**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  
10/06/2016

**From:** Milstein, Judit  
**To:** [Cindy Martin \(cmartin@eriepharma.com\)](mailto:cmartin@eriepharma.com)  
**Subject:** Your NDA 208254-Rhopressa-Request for CMC Information  
**Date:** Tuesday, October 04, 2016 3:29:00 PM

---

With regard to your NDA 208254, please contact your proposed drug product manufacturer to confirm that the manufacturing lines proposed in your submission are currently ready for inspection. If the lines are not ready for inspection, please provide dates for when the lines will be ready.

In order to continue with the timely review of your submission, we request that you respond to this information request no later than October 14, 2016.

Let me know if you have any questions.

Thank you

Judit Milstein

Chief, Project Management Staff

DTOP/OAP/CDER

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6180

Silver Spring, MD 20993

Phone: 301-796-0763

Fax: 301-796-9881

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

/s/

-----  
JUDIT R MILSTEIN  
10/13/2016  
NDA 208254-CMC information request



NDA 208254

**NDA ACKNOWLEDGMENT**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

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

Name of Drug Product: Rhopressa (netarsudil ophthalmic solution), 0.02%

Date of Application: August 29, 2016

Date of Receipt: August 30, 2016

Our Reference Number: NDA 208254

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 October 29, 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](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Judit Milstein  
Chief, Project Management Staff  
Division of Transplant and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

/s/

-----  
JUDIT R MILSTEIN  
09/21/2016  
NDA 208254 Acknowledgment Letter



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 113064

**MEETING MINUTES**

Aerie Pharmaceuticals Inc.  
Attention: Cindy Martin  
Director, Regulatory Affairs  
2030 Main St STE 1500  
Irvine, California 92614

Dear Ms. Martin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AR-13324 Ophthalmic Solution.

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2015. The purpose of the meeting was to discuss API and drug product registration lot stability data, specifications, process validation, and post approval submissions plans, and other CMC information to be provided in the original NDA.

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 questions, call me, at 240-402-8578.

Sincerely,

*{See appended electronic signature page}*

Erin Andrews, Pharm.D  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** December 17, 2015 at 10:00 am to 11:00 am, EST  
**Meeting Location:** Telephone conference meeting (firm requested a telephone conference in lieu of the originally scheduled face to face meeting)

**Application Number:** IND 113064  
**Product Name:** AR-13324 Ophthalmic Solution 0.02%  
**Indication:** Treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.  
**Sponsor/Applicant Name:** Aerie Pharmaceuticals Inc.

**FDA ATTENDEES**

Anamitro Banerjee, PhD	CMC Lead
Sithamalli Chandramouli, PhD	Drug Substance Reviewer
Nancy Waites, MS	Process Reviewer
Navdeep Bhandari, Pharm.D	Regulatory Business Process Manager
Erin Andrews, Pharm.D	Regulatory Business Process Manager
George Lunn, PhD	Drug Product Reviewer
David Bateman, PhD	Microbiology Reviewer
Wiley Chambers, MD	Supervisory Medical Officer
William Boyd, MD	Clinical Team Leader
Rhea Lloyd, MD	Medical Officer

**SPONSOR ATTENDEES**

Tom Mitro	President and Chief Operating Officer
Casey Koczynski, PhD	Chief Scientific Officer
Ken Ruettimann, PhD	Vice President, Manufacturing
Mitchell A. deLong, PhD	Vice President, Chemistry
Ramesh Krishnamoorthy, PhD	Vice President, Drug Product Manufacturing
Mike McClure, PhD	Director, API Manufacturing
Meg Thompson, PhD	Director, Analytical Chemistry
Marvin Garrett	Vice President, Regulatory Affairs & Quality
Cindy Martin	Director, Regulatory Affairs
Anju Parmar	Manager, Regulatory Affairs
Ted Wheeler	Director, Quality Assurance
Carrie Ngangngang	Electronic Submission Specialist, Reg. Affairs

## 1.0 BACKGROUND

AR-13324 is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. Its physicochemical characteristics were engineered specifically for efficient topical ocular delivery. In both rabbit and monkey studies, AR-13324 produced large reductions in IOP with a longer duration of action than reported for previously characterized Rho kinase inhibitors. AR-13324 Ophthalmic Solution has also been shown to provide significant IOP lowering in humans when dosed once daily in the evening, with the most commonly observed adverse event (AE) being transient hyperemia of the conjunctiva.

## 2.0 DISCUSSION

The Agency sent preliminary responses on December 8, 2015, to the Sponsor. The Sponsor provided a response (attached below) on December 15, 2015, and asked to focus on questions 5, 7, and 8.

## 3.0 QUESTIONS

### Question 1

**Does the Agency agree no additional studies are required to determine the fate of starting material impurities?**

#### FDA Response

Yes, the agency agrees that additional studies are not required to determine the fate of starting material impurities.

There is a sufficient number of processing steps and (b) (4)  
(b) (4) which is well above any individual impurity levels seen and the total impurity level.

There is a sufficient number of processing steps and (b) (4)  
(b) (4) to justify not doing additional studies to determine fate of starting material impurities.

(b) (4) You commit to have extraordinarily tight specifications for this starting material. Given that commitment, the (b) (4) protocol practiced, release testing specifications and batch data so far for this material, this approach is acceptable.

Please ensure that the specifications for the starting materials and the justification you have provided in this meeting package are included in the NDA. Further determination has to be made at the time of the NDA review.

**Discussion:**

This topic was not discussed.

**Question 2**

Does the Agency agree with the proposed commercial specification tests and limits for AR-13324 drug substance?

**FDA Response**

Your proposed specification tests for commercial batches and specification limits appear reasonable. Please note that the drug substance specifications is an NDA review decision. Please ensure that the proposed limits are justified in the NDA.

**Discussion:**

This topic was not discussed.

**Question 3**

Does the Agency agree the specification for the [REDACTED] (b) (4) [REDACTED] is adequately justified?

**FDA Response**

The Division agrees with the justification for the proposed specification of [REDACTED] (b) (4) for the sum of [REDACTED] (b) (4).

**Discussion:**

This topic was not discussed.

**Question 4**

Does the Agency agree no additional assessments of potential DNA Reactive (Mutagenic) impurities are required?

### **FDA Response**

Yes, it seems reasonable not to do additional assessments for mutagenic impurities based on the data presented. However, if there is a change in the synthesis route or if there is a process modification this question may have to be revisited during the NDA review.

### **Discussion:**

This topic was not discussed.

### **Question 5**

Does the Agency agree with the drug substance stability data plan for the original NDA submission? Specifically, does the Agency agree Aerie can file the NDA with the available registration lot stability data; i.e., one lot with (b)(4) months, one lot with (b)(4) months, and one lot with (b)(4) months?

### **FDA Response**

PDUFA V requires a complete NDA package at the time of submission. Any additional data (e.g. stability data) should be provided within 30 days of the submission.

*Note: Please refer to page 42 of meeting package – The proposed long term storage condition appears to be mistyped as (b)(4) °C, instead of the intended (b)(4) °C.*

Does the Agency agree the registration and supportive stability data available at the time of NDA submission would be supportive of a (b)(4) month retest date for the drug substance?

### **FDA Response**

This would be a NDA review decision. Please see response to the question above.

### **Discussion:**

The FDA stated (b)(4) months stability data on 3 API lots is required for NDA review (third API lot no later than 30 days). FDA stated that if any stability data become available after NDA submission the information should be submitted. FDA will determine if the data can be included in the review.

### **Question 6**

Does the Agency agree with the proposed drug substance commercial lot stability protocols for the first three commercial production (Process Validation) batches and annual lots thereafter?

**FDA Response**

The Division of Microbiology Assessment agrees with the proposed bioburden testing at initial, 12, 24, and 36 months with optional testing at 48 and 60 months. Your proposed stability protocols seem reasonable. This will have to be further evaluated during the NDA review.

**Discussion:**

This topic was not discussed.

**Question 7**

Does the Agency agree with the proposed drug product specification tests and limits? Does the Agency agree AET testing is not required at release nor annually on commercial stability lots?

**FDA Response**

The drug product specification is an NDA review decision. However, you appear to be testing appropriate parameters. We recommend that the specification for Any Unknown Impurity be (b) (4)%. We agree that antimicrobial effectiveness test (AET) is not required at release; however failure of the AET prior to expiry is a potential safety issue. Thus it is recommended that AET be included as a routine stability test for the commercial drug product at the expiry and periodic intervals, as appropriate. A justification of the tests, methods, and acceptance criteria should be provided in the NDA.

Please confirm that the fill volume will be controlled by (b) (4) testing.

**Discussion:**

FDA stated Aerie's initial proposal setting the unspecified impurity limit at (b) (4)% is NOT acceptable. The limit of (b) (4)% or less of the unknown impurity shall be deemed as acceptable. FDA advised the firm to determine impurities that are above the recommended limit for they are no longer a part of the unspecified. FDA requested long term data in addition to the short term data submission.

FDA provided guidance that AET testing is not needed at release. Aerie agreed to perform AET testing on all commercial stability lots at 12, 24 and 36 months and at expiry, annually.

Aerie confirmed that the fill volume will be controlled by (b) (4) testing.

### **Question 8**

Does the Agency agree with Aerie's overall proposed drug product process validation manufacturing plan? Does the Agency agree with Aerie's proposal for the commercial stability study plans?

### **FDA Response**

FDA does not approve process validation plans and strategies used for process validation studies. The process validation will depend on multiple factors such as actual facility, utilities, qualified equipment, process parameters, control strategies and the trained personnel, some of which are specific to the complexity of the product and manufacturing process. The actual protocols, acceptance criteria, execution, and study outcomes will be evaluated during application review and manufacturing facility inspections. For additional information, please refer to "Guidance for Industry, Process Validation: General Principles and Practices".

A (b) (4) validation study to support the (b) (4) required to (b) (4) the proposed maximum commercial batch size of (b) (4) should be included in the NDA application.

### **Discussion:**

The FDA asked for the commercial stability lots' drug product orientation justification in the NDA with supporting data. Provide this information at the beginning so the data is easily seen by the reviewer and not lost amongst the other supporting details. Data shall be evaluated during the NDA review.

The FDA stated that additional response to this Question would be provided in the official meeting minutes as "Post Meeting Comments".

### **Question 9**

Does the Agency agree the drug product registration and supportive stability data available at the time of NDA submission would be supportive of a 24 month expiration date for the commercial (i.e. NLT 2.5 mL) and sample (i.e. approximately (b) (4)mL) presentations?

### **FDA Response**

The expiration dating period is an NDA review question and will be decided based on a review of the data. We would consider a 24 month expiration dating period. We note that you will be supplying 12 months of long-term stability data for 3 registration batches at the time of NDA submission.

### **Discussion:**

This topic was not discussed.

### **Question 10**

Does the Agency agree that if the drug product cap color changes after approval from white to an AAO recommended cap color, it would be acceptable for the Sponsor to file the cap color change as a CBE-30 supplement? Does the Agency agree with the information to be provided in the CBE-30 supplement?

### **FDA Response**

The proposed change should be submitted as a prior approval supplement. We would encourage discussing the specific color change with the Agency prior to submission of the supplement. When submitted, the supplement should include a full description of all changes and the results of all related testing, an extractables study on the new cap, testing to be in compliance with USP <87> and <661> and revised labeling. You should also propose to conduct leachables testing on stability for the first commercial lot in both fill sizes manufactured with the new cap color.

### **Discussion:**

This topic was not discussed.

### **Post Meeting Comments:**

It is acceptable to provide a detailed summary of the drug substance and drug product process validation studies to be conducted within the NDA submission. Consider including sufficient detail to allow for a sound understanding of your proposed process validation studies. This may include details such as critical in-process parameters and critical manufacturing parameters (for example - time, temperature, RPMs, bioburden, etc.), in-process testing to be performed, and specifications / acceptance criteria ranges for testing and critical parameters. Process validation protocols and reports should be on-site and available for review during the pre-approval inspection.

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

/s/  
-----

ERIN D ANDREWS  
01/14/2016



IND 113064

**MEETING MINUTES**

Aerie Pharmaceuticals, Inc.  
Attention: Marvin J. Garrett  
Vice President, Regulatory Affairs and Quality  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Mr. Garrett:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AR-13324 ophthalmic solution, 0.02%.

We also refer to the meeting between representatives of your firm and the FDA on October 27, 2015. The purpose of the meeting was to discuss Phase 3 efficacy and safety results and other clinical information to be provided in the original NDA.

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 Eithu Lwin, Regulatory Project Manager at (301) 796-0728.

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



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 27, 2015, 11:00 AM– 12:00 PM (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**Application Number:** IND 113064  
**Product Name:** AR-13324  
**Indication:** Treatment of elevated intraocular pressure  
**Sponsor/Applicant Name:** Aerie Pharmaceuticals, Inc.

**Meeting Chair:** Wiley A. Chambers  
**Meeting Recorder:** Eithu Z. Lwin

**FDA ATTENDEES**

Renata Albrecht/ Division Director  
Wiley A. Chambers/ Deputy Division Director  
Sonal Wadhwa/ Clinical Reviewer  
Lucious Lim/ Clinical Reviewer  
Rhea Lloyd/ Clinical Reviewer  
Yan Wang/ Statistics Team Leader  
Solomon Chefo/ Statistics Reviewer  
Philip Colangelo/ Clinical Pharmacology Team Leader  
Yongheng Zhang/ Clinical Pharmacology Reviewer  
Lori Kotch/ Nonclinical Team Leader  
Maria Rivera/ Nonclinical Reviewer  
Mary Lewis/ Nonclinical Reviewer  
Roy Blay/ Office of Scientific Investigations (by phone)  
Eithu Z. Lwin/ Regulatory Health Project Manager

**EASTERN RESEARCH GROUP ATTENDEES**

ERG Marc Goldstein, Independent Assessor

**SPONSOR ATTENDEES**

Tom Mitro/ President & Chief Operating Officer  
Theresa Heah/ Vice President, Clinical Research and Medical Affairs

Casey Kopczynski/ Chief Scientific Officer  
Marvin Garrett/ Vice President, Regulatory Affairs and Quality  
Cindy Martin/ Director, Regulatory Affairs  
Richard Lewis/ Chief Medical Officer (by phone)  
Sushanta Mallick/ Vice President, Clinical Research/Glaucoma (by phone)  
Jon Williams/ Director, Clinical Trial Management (by phone)  
Mini Balaram/ Medical Director, Clinical and Medical Affairs (by phone)  
Jeanine Gouveia/ Manager, Regulatory Affairs (by phone)  
(b) (4) Aerie Consultant  
(b) (4) Aerie Consultant

## BACKGROUND

Aerie Pharmaceuticals, Inc. submitted a meeting request on August 4, 2015, received August 5, 2015, requesting a Pre-NDA meeting to discuss Phase 3 efficacy and safety results and other clinical information to be provided in the original NDA. The Division issued a Meeting Request Granted letter on August 17, 2015, granting a Type B, Pre-NDA meeting for October 27, 2015.

The Division issued preliminary comment in response to the question posted in the September 25, 2015, briefing package on October 21, 2015. On October 26, 2015, Aerie provided their responses to our preliminary comments and stated that that further discussion is needed on questions 1, 2, 3, 9 and 10, reach agreement on content of complete application and discuss on need for REMS.

## DISCUSSION

For the purposes of these minutes, the question posted in the briefing document are in **bold** format, our preliminary response issued are in *italics*, Sponsor responses provided on October 26, 2015, email are in ***bold italics***, and the meeting discussions are in normal font.

## CLINICAL

1. **Efficacy data are available for two Phase 3 trials, AR-13324-CS301 (QD PM dosing only) and AR-13324-CS302 (QD PM and BID AM/PM dosing). While the CS301 Phase 3 trial did not demonstrate non-inferiority of AR-13324 to timolol for the primary analysis in patients with mean baseline IOP below 27 mmHg, the trial showed non inferiority of AR-13324 to timolol in patients with mean baseline IOP below 25 mmHg. In the second Phase 3 trial, AR-13324-CS302, AR-13324 dosed QD and BID met non inferiority to timolol for the primary analysis in patients with mean baseline IOP below 25 mmHg. In addition, in AR-13324-CS302, only the BID dosing regimen met non inferiority to timolol for the secondary analysis in patients with mean baseline IOP below 27 mmHg.** (b) (4)

**Does the Agency agree with the Sponsor's NDA filing plans?**

*FDA Response: No. It does not appear that there would be a sufficient safety database to support an NDA based on the results of CS301 and CS302 alone. If additional studies are*

*intended to supplement the safety database, the completed study reports of these additional studies should be included in an NDA submission.*

**Aerie Response:**

***In both CS301 and CS302 studies AR-13324 Ophthalmic Solution 0.02% met non-inferiority to timolol in subjects with baseline IOP <25 mmHg when dosed QD, and also when dosed BID in CS302.***

***By our estimate, at time of NDA submission, we plan to have at least 500 patients exposed to AR-13324 0.02% QD or higher. At least 100 of these subjects would be exposed for 12 months on AR-13324 0.02% QD as discussed and agreed to at our 11 April 2014 EOP2 meeting.***

***Does the Agency agree that the safety data available for QD dosing is acceptable for an NDA submission to obtain approval for this dosing regimen?***

***See Aerie response to Question 2 for additional discussion on QD and BID.***

**Meeting Discussion:** The Division stated that providing safety data for at least 500 patients exposed to AR-13324 ophthalmic solution, 0.02% QD or higher and at least 100 of these subjects exposed for 12 months or longer, is likely to be sufficient for NDA filing as long as those data are from completed studies and are presented within their respective final clinical study reports.

- 2. The 3-month safety data currently available for the Phase 3 AR-13324-CS302 trial (QD PM and BID AM/PM dosing) show that the AR-13324 0.02% BID dosing regimen had a substantially higher rate of premature discontinuations due to adverse events than did the QD dosing regimen (30.3%, 77/254 vs. 12.4%, 31/251, respectively). As well, the AR 13324 0.02% BID dosing regimen produced more subjects with ocular adverse events than did the QD dosing regimen (78.3%, 198/253 vs. 64.9%, 163/251, respectively). These safety data, together with the relatively similar ocular hypotensive efficacy of both dosing regimens (presented in Section 10 of the meeting package) demonstrate that QD dosing of AR 13324 is optimal due to a better benefit-risk ratio than BID dosing.**

(b) (4)

**Does the Agency agree?**

***FDA Response: Based on the information that you have submitted to date,***

(b) (4)

***is a review issue after the complete study reports have been submitted and reviewed.***

**Aerie Response:**

***With regard to efficacy, in both CS301 and CS302 AR-13324 Ophthalmic Solution 0.02% met non inferiority to timolol in subjects with baseline IOP <25 mmHg when dosed QD and BID in CS302. Looking just at mean IOP, the BID dosing was somewhat more effective. However, the efficacy difference between QD and BID for subjects with baseline***

***IOP <25 mm Hg was <1 mmHg at 7 of 9 time points. The difference in mean diurnal IOP between QD and BID dosing was approximately 0.5 mmHg.***

***With respect to safety, there was a notable difference in the safety profiles between QD and BID. The BID dosing regimen had a high rate of premature discontinuations due to adverse events, 30.3%, compared to 12.4% for QD dosing. As well, the AR 13324 0.02% BID dosing regimen produced more subjects with ocular adverse events than did the QD dosing regimen (78.3% vs. 64.9%, respectively).***

***As requested by FDA, we evaluated BID dosing. Due to the high adverse event-related discontinuation rate for BID dosing, we expect to have fewer than 100 BID subjects with 12 months safety data in the NDA submission. We estimate we will be able to provide 12 months safety data for approximately 70 BID subjects in the original NDA, which will include the final CSR for CS301*** (b) (4)

***However, we suggest that the 3 month data from CS302 provide sufficient information on BID dosing to conclude that increased exposure to AR 13324 provides minimal additional benefit, and increased risk, relative to QD dosing.*** (b) (4)

***Does the FDA agree that submitting 3 months of safety and efficacy data on more than 150 BID subjects, and 12 months of safety data on less than 100 BID subjects, will be sufficient to fulfill the FDA's request for information on BID dosing of AR-13324?***

***Meeting Discussion:*** The Division stated that complete study reports for both AR-13324-CS301 and AR-13324-CS302 are needed to adequately review efficacy and safety of QD vs. BID dosing. Patients derived from studies which are not complete (i.e., in which all patients in that particular study have not yet met their 3 or 12 month evaluations (as described in the respective study)) would not be considered to meet the minimum expectation for the number of patients studied.

- 3. In the initial NDA the Sponsor intends to provide at least 500 subjects exposed to the intended dose (AR-13324 Ophthalmic Solution 0.02% QD) or higher. Of these subjects, at least 100 will be exposed to the intended dose for 12 months. These subjects are expected to be from Study AR-13324-CS302, though some subjects could be from the 12-month safety study AR-13324-CS303. In addition, the Sponsor plans to have at least 100 subjects meeting this exposure criterion from the timolol maleate ophthalmic solution 0.5% BID treatment group.***

***Does the Agency agree with the Sponsor's NDA filing plans?***

***FDA Response:*** We agree provided that the full study report for AR-13324-CS303 will be included in the submission.

***Aerie Response:***

***The Canadian 12-month safety study AR-13324-CS303,*** (b) (4)  
***was initiated in 3rd quarter 2014. As of 21 October 2015, we have enrolled a total of 87 out of 240 planned subjects in this 3-arm study (AR-13324 QD and BID; Timolol BID) due to slow study enrollment. The projected study completion will occur well after NDA submission; and therefore, the final clinical study report will not be available. Masked safety information will be filed in the original NDA and in the 4 month***

***safety update for this ongoing trial. Additionally, Aerie plans to stop any new enrollment in this study due to the slow enrollment.***

Meeting Discussion: The Division stated that if there are sufficient number of subjects for the safety evaluations from completed studies AR-13324-CS301 and AR-13324-CS302 and if those completed CSRs are submitted in the original NDA, then the plan to submit masked safety data for ongoing study CS303 at the time of the NDA submission and followed up with the 120-day safety update would be sufficient.

- 4. For the AR-13324 NDA, the Sponsor proposes reporting and grouping adverse events by total adverse events, by ocular adverse events, and by non-ocular adverse events.**

**When summarizing adverse events within the NDA and as a resource for an anticipated discussion of labeling with the Agency, the Sponsor proposes to focus on ocular or non-ocular adverse events that occur at a frequency  $\geq 1\%$ , using treatment group data integrated across all AR-13324 Phase 3 clinical studies (i.e., CS301, CS302, and other relevant studies) over the first 3 months of treatment.**

**If this proposal is acceptable, the Sponsor intends to group ocular adverse events occurring at frequencies of 1-4%, those occurring at frequencies of 5-10%, and then separately mentioning those adverse events that occur at a frequency greater than 10%.**

**Does the Agency agree with this proposal?**

*FDA Response: We request that you report all ocular and non-ocular AEs that occur for each study separately and for treatment group data integrated across all AR-13324 Phase 3 clinical studies, regardless of frequency or relationship to use of the study product.*

Meeting Discussion: None

- 5. The NDA submission for AR-13324 Ophthalmic Solution 0.02% will provide a comparison of efficacy data for the AR-13324-CS301 and CS302 clinical studies and of the pooled efficacy data (for equivalent treatment arms) as appropriate.**

**Does the Agency accept this approach?**

*FDA Response: Acceptable.*

Meeting Discussion: None

- 6. The statistical analysis plans for the Phase 3 AR-13324-CS301 and -CS302 studies individually require that the primary efficacy analyses be conducted with the Per Protocol (PP) population, not the intent to treat (ITT) population. This topic was discussed with the FDA at the 11 April 2014 End of Phase 2 meeting. The Sponsor recognizes that the Agency is interested in additionally receiving the primary efficacy analyses on the ITT population. The Sponsor plans to provide the primary efficacy analyses and select secondary efficacy analyses for the individual studies, as well the integrated data analyses, primarily on the PP analysis population and secondarily on the ITT analysis population.**

**Does the Agency agree to this plan?**

*FDA Response: Regardless of which analysis is the primary and which is the secondary, the Agency expects the ITT and PP analyses to have similar results; if not you will be expected to justify why there are discrepancies.*

*Additionally, please provide analysis results for the change from baseline in IOP at each time points of each visit using both analysis populations.*

Meeting Discussion: None

- 7. The statistical analysis plans for the Phase 3 AR-13324-CS301 and CS302 studies individually describe subgroup analyses for the primary efficacy variable by subject demographics [age: <65 and ≥65 years; gender: males and females; race: Caucasian and other; and iris color: blue/grey/green, brown/black and hazel], maximum baseline IOP value [<22 mmHg, <23 mmHg, <24 mmHg, and <26 mmHg], and two different categorizations of prior hypotensive medication experience [1) combination therapy, prostaglandin (monotherapy), other (monotherapy), and no prior therapy; and 2) prior prostaglandin and no prior prostaglandin]. The Sponsor additionally proposes to provide integrated efficacy and safety summaries for these subgroups in the NDA submission.**

**Does the Agency agree with this plan?**

*FDA Response: Acceptable.*

Meeting Discussion: None

- 8. The Sponsor recently commenced a fourth Phase 3, double-masked, randomized, multi-center, 2-arm study to generate additional confirmatory data on the safety and ocular hypotensive efficacy of AR-13324 Ophthalmic Solution 0.02% dosed QD in the evening. This study is a 6-month trial with a primary efficacy analysis at 3 months in patients with mean baseline IOPs below 25 mmHg and secondary efficacy analysis in patients with mean baseline IOP below 27 mmHg. Masked safety information will be filed in the original NDA and in the 4 month safety update for this ongoing trial.**

**Does the Agency agree with this approach?**

*FDA Response: The Agency expects the NDA submission to be complete at the time of submission. Additional information submitted during the review cycle may not be reviewed.*

Meeting Discussion: None

- 9. Based on the approved initial Pediatric Study Plan (iPSP), the Sponsor attempted to enroll subjects 0-2 years of age who fit the Inclusion/Exclusion criteria in the completed AR-13324-CS301 study and in the ongoing AR-13324-CS302 study at a large number of clinical investigator sites where such subjects are known to be part of the clinic patient population. However, the Sponsor has been unsuccessful in enrolling any subjects in this age group. Of note, the Sponsor has enrolled 2 pediatric subjects aged 11 and 14 years in study AR-13324-CS302 and will present the pediatric data gathered from these subjects in the NDA. Given the above, the Sponsor submits that all pediatric study requirements are complete and no further pediatric studies (subjects 0-17 years of age) are required on AR-13324 Ophthalmic Solution 0.02%.**

**Does the Agency agree with this approach?**

***FDA Response:** You will need to provide a detailed explanation within the application of the attempts to enroll pediatric patients and their results. The Agency will need to review this information prior to determining whether the requirements for pediatric studies have been met or that all pediatric study requirements are complete.*

***Aerie Response:***

***We amended the CS301 and CS302 study protocol to include 60 subjects 0-2 years old (instead of subjects aged 2-17 years as originally proposed), in accordance with our agreed upon Pediatric Study Plan dated 8 August 2014. To ensure adequate recruitment of pediatric subjects, we had study sites where the patient population included sufficient numbers of pediatric patients in both CS301 and CS302. This information is summarized in the Table below.***

Study	# of Sites Reporting >15 Pediatric Glaucoma Patients per Month	Additional Comment
CS301	7 of 37	Of these, one site reported an average of >100 pediatric glaucoma patients/month
CS302	13 of 62	Of these, 2 sites reported an average of >100 pediatric glaucoma patients/month

***In spite of these measures, we were unable to enroll any pediatric subjects in the 0-2 year age group.***

***In our estimation, the Inclusion and Exclusion criteria for the pediatric subjects in the approved iPSP were quite challenging to meet.***

***In particular,***

- the inclusion criterion requiring that patients must not be on another IOP lowering medication for at least 30 days prior to entry into the study. And, if they are on another medication, and the investigator determines that it is safe to do so, the patient may be washed out from the prior medication and screened for entry into the trial,***
- the exclusion criterion of the presence of any condition or concern by the investigator that participating in the trial would be a safety risk for the patient, need for multiple examinations under anesthesia or ocular/systemic pathologies or co-morbidities that enhance the risk to the patient.***

***Additionally, the limited safety information with pediatric use of the comparator timolol 0.5% ophthalmic solution and the fact that there is consensus in published scientific literature advocating against its use in neonates and infants for whom lower concentrations of timolol ie, 0.25% or 0.1% [as available], are preferred, may also have contributed to our lack of success with enrollment of subjects aged 0-2 years.***

***Does the Agency agree that we have made a concerted effort to enroll subjects aged 0-2 years in our pivotal trials and that no additional pediatric studies are required for submission and review of the NDA?***

Meeting Discussion: The Division stated that the available pediatric data should be submitted with the NDA for review, and the Sponsor can consider a request for a waiver in the NDA, providing reasoning for not having pediatric patients. The Agency will review the information and determine whether the requirements for pediatric studies have been met, a waiver is appropriate, or if a Post-Marketing Requirement (PMR) Phase 4 pediatric study is needed.

**10. Corneal deposits, often described by investigators as “corneal whorls” or “corneal verticillata,” were reported as an adverse event associated with AR-13324 Ophthalmic Solution 0.02% treatment (QD and BID). Drug-induced corneal verticillata are commonly seen in patients on amiodarone therapy and arise from phospholipidosis (accumulation of phospholipids in lysosomes). Like amiodarone and other drugs known to induce phospholipidosis, AR-13324 is a cationic amphiphilic drug (CAD) that contains a hydrophobic ring structure and a hydrophilic side chain with a charged amine group. To determine whether the AR-13324-associated corneal deposits are a result of phospholipidosis, the Sponsor is investigating the ability of AR-13324 to induce lysosomal accumulation of phospholipids in tissue culture cells at physiological drug concentrations, using an assay that has been validated for identifying drugs that induce phospholipidosis in vivo. If the assay results are positive, the Sponsor believes this will provide sufficient nonclinical characterization of the etiology of the corneal deposits to support the filing of the NDA.**

**Does the Agency agree with this approach?**

FDA Response: *We agree that the assay appears adequate to determine whether AR-13324 induces phospholipidosis. However, a final decision regarding adequacy of the assay/data to support your conclusions cannot be reached until the study report is reviewed.*

*The development of deposits in the cornea may have an impact on visual function. The development and new drug application of AR-13324 (and any related molecules) should include evaluations of the short term and long term potential of the drug product to impair visual function (not just visual acuity).*

Aerie Response:

***Thank you for your response. A full study report will be submitted with the NDA. As a point of clarification, does the Agency agree that this in vitro approach is sufficient to characterize the etiology of the corneal deposits for the NDA submission?***

***We are making every effort to continue surveillance to resolution in subjects with corneal deposits. Visual function testing in the form of periodic visual acuity testing and visual fields at study entry and exit are conducted for all subjects including those with corneal deposits in both CS301 and CS302. The corneal deposits were typically seen only upon biomicroscopy. They were asymptomatic and did not affect visual acuity or visual fields.***

***Does the Agency agree that the above tests are adequate?***

Meeting Discussion: The Sponsor asked for clarification if the *in vitro* approach is sufficient to characterize the etiology of the corneal deposits for the NDA submission. The Division

responded that assuming the *in vitro* study report is found adequate, no additional non-clinical data is likely to be needed, but those results are unlikely to address all of the clinical concerns.

The Division stated that visual acuity and visual field examinations are not adequate by themselves to fully assess visual function in subjects with corneal deposits and recommended the Sponsor to consider investigating contrast sensitivity and glare testing to further assess visual function. If there are remaining issues during NDA review, a Phase 4 post-marketing commitment may be required to further assess potential effects of corneal deposits on visual function.

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our August 17, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

Meeting Discussion: The Sponsor requested clarification or examples of ‘minor application components’ that could be submitted within 30 days after submission of the original application. The Division stated one example could be (b) (4)-month stability data for the drug substance or drug product. Additional examples of items that could be submitted within 30 days of original submission are articles requiring translation that were not available for the original submission and a change in color of the carton and the printer could not have this ready for the original submission. The Division recommended that the Sponsor submit formal requests for these minor

component submission and reach prior agreement with the Division that these items would be submitted within 30 days after the original submission.

The Sponsor asked if a REMS would be required for this NDA, and the Division responded that nothing has been identified at this time that would require a REMS for the NDA.

A Chemistry Manufacturing and Controls (CMC) pre-submission meeting is scheduled for December 17, 2015. A summary of agreements reached at that meeting will be documented in separate minutes.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR). 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 related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**ISSUES REQUIRING FURTHER DISCUSSION**

None

**ACTION ITEMS**

None

**ATTACHMENTS AND HANDOUTS**

None

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

/s/  
-----

WILEY A CHAMBERS  
11/19/2015



IND 113064

**MEETING MINUTES**

Aerie Pharmaceuticals, Inc.  
Attention: Brian Levy, O.D., M.S.  
Chief Medical Officer  
135 Route 206  
Suite 15  
Bedminster, NJ 07921

Dear Dr. Levy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AR-13324 Ophthalmic Solution.

We also refer to our May 6, 2014, minutes of the End of Phase 2 meeting held between representatives of your firm and the FDA on April 11, 2014. Those minutes contained a typographical error in the Agency's response to Question 2 in the Post-Meeting Addendum. Paragraph 2 of that response should have read, [REDACTED] (b) (4)

[REDACTED] The attached minutes have been revised with the correct statement.

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  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Date/Time:** April 11, 2014, 9:00 am

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 21, Conference Room: 1315  
Silver Spring, Maryland 20903

**Meeting Type:** Type B – End of Phase 2

**Application:** IND 113064

**Drug:** AR-13324 Ophthalmic Solution

**Sponsor:** Aerie Pharmaceuticals, Inc.

**Indication:** For reduction of elevated intraocular pressure

**Meeting Chair:** Wiley Chambers  
**Meeting Recorder:** Michael Puglisi

### FDA PARTICIPANTS:

Edward Cox/ Director, Office of Antimicrobial Products  
Wiley Chambers/ Deputy Division Director  
William Boyd/ Clinical Team Leader  
Martin Nevitt/ Medical Officer  
Jennifer Harris/ Medical Officer  
Maria Rivera/ Nonclinical Reviewer  
Lori Kotch/ Nonclinical Team Leader  
Balajee Shanmugam/ Product Quality Team Leader  
Dongliang Zhuang/ Statistics Reviewer  
Yan Wang/ Statistics Team Leader  
Yoriko Harigaya/ Clinical Pharmacology Reviewer  
Philip Colangelo/ Clinical Pharmacology Team Leader  
Michael Puglisi/ Regulatory Project Manager

### SPONSOR PARTICIPANTS:

Marvin J. Garrett/ Vice President, Regulatory and Quality Assurance  
Casey Kopczynski/ Chief Scientific Officer  
Brian Levy/ Chief Medical Officer  
Thomas Mitro/ Chief Operating Officer  
(b) (4) / Consultant, Pharmacology, Toxicology, and Chemistry  
(b) (4) / Consultant, Clinical and Regulatory  
Dale W. Usher/ Vice President, Statistics  
Ramesh Krishnamoorthy/ Vice President, Manufacturing  
(b) (4) / Consultant, Chemistry

**MEETING OBJECTIVE:**

To discuss the Sponsor's plans for the Phase 3 program and eventual NDA submission for AR-13324 for reduction of elevated intraocular pressure.

**SUMMARY OF DISCUSSION:**

Agency responses to the questions outlined in the March 4, 2014, background package (see bolded text below) were provided to the Sponsor in an email dated April 4, 2014, (see text in italics below). This meeting served to clarify those responses. The discussion during the meeting is reflected in normal font.

**QUESTIONS FOR DISCUSSION:**

- 1. Pharmacology and Clinical: Based upon the completed safety pharmacology, genotoxicity, systemic and ocular toxicology studies, and the 3-month interim reports for the rabbit and monkey long-term ocular toxicology studies, the Sponsor believes they have sufficient nonclinical data to support initiation of the planned Phase 3 studies (AR13324-CS301 and AR13324-CS302). Furthermore, the Sponsor believes that receipt of audited final pathology reports from the ongoing rabbit and monkey long-term ocular toxicology studies will support dosing beyond 3 months for AR-13324-CS302. Does the Agency agree?**

*Agency Response: According to the briefing document, you have conducted ocular toxicity studies of 3/6 month duration in rabbits and 3/9 month duration in monkeys that, pending review, can support chronic dosing in humans. However, the study reports submitted to the Division are of up to 28-day duration. To support clinical trials of 1-3 months duration, the 3-month interim data including full histopathology data should be submitted for review. To support dosing in humans beyond 3 months, the full study reports for the 6-month rabbit and 9-month monkey studies should be submitted for review.*

Meeting Discussion: The Sponsor stated they have recently submitted the interim reports for the 6-month rabbit and 9-month monkey studies and noted that the rabbit 3-month interim report is labeled as draft, but this is a final interim report. This is due to the Standard Operating Procedure of that facility. The Agency agreed this is acceptable.

- 2. Pharmacology and Clinical: Based upon the completed, in process and planned safety pharmacology, genotoxicity and systemic and ocular toxicology studies, the Sponsor believes they will have sufficient nonclinical data to support approval of an NDA for chronic use. Note that the longest period of systemic dosing was 28 days, i.v. in rats and dogs (Studies AR-13324-AS09 and AR-13324-AS10). Does the Agency agree?**

*Agency Response: We agree that the battery of nonclinical studies appear sufficient to support submission of the NDA. However, the adequacy of the studies planned to be submitted with the NDA or the need for additional nonclinical studies to support approval will be a review issue.*

Meeting Comment: There was no discussion of this matter during the meeting.

3. **Pharmacology and CMC:** The (b) (4) being used to manufacture drug substance (API) for Phase 3 clinical studies is not expected to contain any new (b) (4) impurities when compared to the API used in the Phase 1/2 clinical studies, while the residual solvents have modestly changed to include (b) (4) as a potential residual solvent. The Sponsor has made API using this (b) (4) to support the ongoing long-term ocular toxicology studies. Further, the formulation composition and the method of manufacture of the drug product formulation have remained unchanged throughout the course of the drug development program to date. The Sponsor proposes not to repeat any previously conducted pre-clinical toxicology studies to qualify API produced from this (b) (4) or drug product made from API produced from this (b) (4). Does the Agency agree that this approach is adequate to demonstrate suitability of the API and drug product presentations for Phase 3 studies through the NDA?

Agency Response: A similar question was previously asked to the Division in the meeting package received on 2-7-14. See response below previously provided under SD # 22 (meeting held on 3-10-14).

*“FDA concurs with this general approach. Please be aware that the adequacy of the ongoing 9-month GLP monkey toxicology study and the 6-month GLP rabbit toxicology study will be review issues, when the reports are received. Please submit the reports for these long-term studies prior to dosing patients longer than supported by the previously-submitted nonclinical studies (i.e. 28 days).*

*Please be aware that the proposed threshold of toxicologic concern (TTC) approach outlines in the meeting package is not applicable to (b) (4). These would be (b) (4) compounds under the draft ICH M7 guidance. For the NDA submission, propose compound-specific acceptable limits based on the available carcinogenicity data.”*

Meeting Discussion: The Sponsor asked about the possibility of using the Phase 2 material for part of the Phase 3 study. The Agency stated the usual recommendation is to perform at least one Phase 3 study with the final, to-be-marketed formulation. Changing the formulation during one of the studies may not be acceptable depending on how the formulations and packaging differ, and the timing of the change. The Agency noted that there appeared to be differences in the manufacturing of the initial batches. For packaging, equivalent drop size is an important factor. It is important to have data on enough patients using the final configuration in the Phase 3 study to determine if there are any container-closure issues. The point in the study at which a change is made is a critical factor in determining whether the change will be acceptable. The Agency agreed to consider a specific proposal by the Sponsor and suggested using the Special Protocol Assessment (SPA) approach, provided an SPA request is submitted prior to the start of the study.

- 4. Pharmacology and Clinical: The Sponsor conducted nonclinical toxicokinetic studies in rats and dogs to assess the systemic exposure to AR-13324, (b) (4) of AR-13324 (b) (4) and their respective primary metabolites (AR-13503 (b) (4), respectively) after systemic administration. In addition, the Sponsor conducted toxicokinetic studies in rabbits and monkeys to assess systemic exposure to AR-13324, (b) (4), AR-13503, (b) (4) after topical ocular dosing. The Sponsor has conducted an evaluation of blood levels of AR-13324 and its active metabolite (AR-13503) in humans after topical administration (Study AR-13324-CS101). Aerie believes that reproductive and carcinogenicity toxicology studies will not be necessary, based upon the extremely low blood levels of AR-13324 and its related compounds following topical ocular administration. Does FDA concur?**

*Agency Response: We recommend you conduct embryo-fetal developmental toxicity studies. Regarding the waiver for carcinogenicity studies, a final determination on the need for these studies cannot be made until the NDA is fully reviewed. Please note that the marketing application can be filed without the carcinogenicity studies. A waiver should be provided to justify the omission of the studies. If needed, it may be acceptable to conduct carcinogenicity studies as a post marketing requirement.*

Meeting Discussion: The Sponsor asked about the dose selection for the embryo fetal study (EFD), noting that severe injection site reactions were dose limiting in general toxicity studies. The Sponsor asked if they can use doses in EFD studies that will allow complete dosing, even if they do not observe maternal toxicity. The Sponsor expects the doses used will provide exposure margins greater than 50-fold the anticipated human exposure after ocular administration. The Agency asked if alternative routes of administration have been explored. The sponsor mentioned limitations with other routes. The Agency stated that in the case that the intravenous injection remains the only option, it is recommended that the Sponsor use the highest feasible dose, and provide discussion in the study report regarding methodology limitations.

- 5. Pharmacology: With respect to pediatric studies, the Sponsor is not planning to conduct any juvenile toxicology studies to support the intended Phase 3 studies (AR-13324-CS301 and AR-13324-CS302) or the NDA. Does FDA concur?**

*Agency Response: Unless a reason of concern arises upon review of the clinical and nonclinical data, we agree studies in juvenile animals are not necessary.*

Meeting Comment: There was no discussion of this matter during the meeting.

- 6. Clinical: The Sponsor has conducted two dose-response Phase 2 studies in patients with elevated intraocular pressure (AR-13324-CS201 and AR-13324-CS202). All dosing of AR-13324 Ophthalmic Solution was once-daily. The Sponsor believes that the 0.02% concentration of AR-13324 Ophthalmic Solution dosed once a day (q.d.) is the optimal dose, and plans to evaluate this as the sole dosage of AR-13324 Ophthalmic Solution in Phase 3, and for intended marketing. Does FDA concur?**

Agency Response: You have not established a time curve for the duration of action of your proposed product. Potential damage due to elevated intraocular pressure is not limited to one portion of the day. It would be important to include a bid dosing arm to establish that your current once a day proposal is not suboptimal dosing. It is also important to inform physicians and patients whether bid dosing is less effective than once a day dosing as seen in some classes of IOP reducing products, or whether bid dosing is more effective than once a day dosing as seen in some other classes of IOP reducing products.

Meeting Discussion: The Sponsor proposed [redacted] (b) (4)  
[redacted] (b) (4)  
The Agency disagreed. [redacted] (b) (4)  
[redacted] (b) (4)  
The Agency disagreed [redacted] (b) (4)

7. **Clinical:** For the Phase 3 Studies AR-13324-CS301 and AR-13324-CS302, the positive control to be used as the comparator will be timolol maleate Ophthalmic Solution, 0.5%, b.i.d., O.U. The Sponsor will mask the identity of the positive control by removing the commercial label and affixing a double-masked investigational product label; the labeled bottles of both timolol and the investigational products will be placed in identical kit boxes which will be masked and labeled in an identical fashion. Further, the proposed container-closure systems used for the AR-13324 product clinical supplies have been chosen to match as closely as possible the generic product presentation of timolol maleate ophthalmic solution, 0.5%. The Sponsor does not plan to perform a sterile transfer of the positive control into the identical bottles used for AR-13324. Neither the investigator nor the patient will be advised as to the treatment assignment. The Sponsor will utilize an FDA-approved generic version, timolol maleate ophthalmic solution, 0.5%. Does FDA concur?

Agency Response: Your proposal to re-label the positive control is acceptable, but you do not propose to control the potential bias related to the different dosing regimens (i.e. b.i.d versus q.d.). We recommend you include bid dosing of your drug product and include both dosing regimens for timoptic to attempt to minimize potential bias in this trial.

Meeting Discussion: The Sponsor confirmed they plan to administer a dummy dose to minimize potential bias.

[redacted] (b) (4)

[redacted] (b) (4)

(b) (4) The Agency stated this did not seem like an unreasonable approach but the Agency would need to have a further discussion of the proposal. A more definitive Agency response would be provided in post-meeting comments.

8. **Clinical:** With regard to the Phase 3 program, one study will be of 3 months treatment duration (AR-13324-CS301), and the other study will be of 12 months treatment duration with a planned interim analysis at 3 months (AR-13324-CS302). Consistent with the Agency's draft guidelines for glaucoma, the studies will be powered to demonstrate equivalency within 1.0 mm Hg at a majority of timepoints, and 1.5 mm Hg at all timepoints (95% confidence intervals,  $\alpha = 0.05$ , two-tailed) in the per protocol population. This evaluation will be conducted at 08:00, 10:00 and 16:00 hours at weeks 2 and 6 and month 3 to include the presumed peak and trough for timolol maleate and AR-13324. To the extent possible the Sponsor will select high enrolling sites, however all randomized, dosed patients will be included in the primary efficacy analyses. Does FDA concur?

*Agency Response:* Yes. We recommend the primary efficacy analyses be based on intent-to-treat population including all randomized subjects. In your protocol outline, the analyses are based on per protocol population.

*For the criteria of testing non-inferiority of  $\leq 1.0$  mm Hg at a majority of time points, if you intend to make formal statistical inference, you need to address multiplicity issues because there are multiple pathways to meet this criterion. If you intend to treat this non-inferiority criterion as only a clinical criterion (which would be acceptable) and without making formal statistical inference, you do not need to address the multiplicity issue. Please clearly state your intent in the protocol.*

**Meeting Discussion:** The Sponsor clarified that the study will be powered to demonstrate non-inferiority, not equivalence as stated in the question. The Agency stated that equivalence is the standard for IOP studies. There was a discussion about the ITT analysis and per protocol analysis. The Agency recommended ITT analysis, but would expect the Sponsor to conduct both analyses and provide explanation if the two analyses yield different conclusions. The Agency clarified that 1.0 mmHg is the clinical criterion and it would be considered only after the study has met 1.5 mmHg criterion. Sponsor asked about the impact of not meeting the clinical criterion on the labeling. The Agency stated that the impact of not meeting the clinical criterion will be a review issue.

9. **Clinical:** The Sponsor plans to submit in the NDA the described clinical studies to support the safety of the compound. The Sponsor plans to enroll 500 patients in the AR-13324 treatment arms in the Phase 3 trials for the 3 month duration of the study. The Sponsor believes that these numbers will ensure that a minimum of 300 patients will be exposed to the intended marketed dosage of AR-13324 Ophthalmic Solution, 0.02%, for 3 months. (b) (4)

*Agency Response: The Agency will not commit [REDACTED] (b) (4)  
[REDACTED] we strongly recommend [REDACTED] (b) (4)*

[REDACTED] (b) (4)

Meeting Comment: There was no discussion of this matter during the meeting.

- 10. Clinical:** The Sponsor intends to evaluate corneal endothelium by specular microscopy in one of the planned Phase 3 studies (AR-13324-CS302). For at least 100 patients, endothelial cell counts will be assessed prior to dosing, and 12 months after commencement of treatment. The Sponsor plans to submit the (b) (4)-month post-treatment specular microscopy information in an update to the NDA (4 month safety update or possibly post-approval). Does FDA concur that sufficient patient numbers and duration of treatment are provided for corneal endothelial requirements?

*Agency Response: The Agency will not commit to review additional data after the original NDA submission; we strongly recommend that the application contain all information necessary to take an action at the time of submission, i.e. endothelial cell count data at month 3. If you are relying on additional safety data to support your application, it should be submitted prior to the filing of the application. You may wish to consider an additional 3 month endothelial cell count evaluation.*

Meeting Discussion: The Sponsor stated they intend to submit the NDA with endothelial cell counts for 100 treated patients plus a control group for at least 3 months. The Agency agreed this is acceptable [REDACTED] (b) (4)

- 11. Pediatric:** In the pre-IND meeting of 31 October 2011, FDA recommended that "...all ages of pediatric patients (0-18) are recommended to be included in clinical trials of intraocular pressure lowering medications unless the expected safety profile of the drug product would lead to unacceptable risks in the pediatric population. In that case, a justification should be provided." The Sponsor plans to allow entry of pediatric patients of ages 2-17 into the Phase 3 clinical trials (AR-13324-CS301 and AR-13324-CS302), with the acknowledgement that some of the evaluations of signs and symptoms may not be possible in younger patients. The Sponsor does not intend to set a quota for pediatric patient enrollment. Given the limited systemic exposure to AR-13324 after ocular administration in adults, the Sponsor expects pediatric patients to have a similar low exposure, and thus does not plan to obtain

**blood samples for bioanalytical assessment in the pediatric population. Does FDA concur?**

Agency Response:

*Yes. We agree that no additional studies are needed to evaluate the systemic PK exposure to AR-13324 after ocular administration of the 0.02% ophthalmic solution in the pediatric population.*

*Your pediatric study plan (PSP) should contain comment on why patients between the ages of 0-2 will be excluded from the proposed trials.*

Meeting Discussion: The Agency reiterated that the Sponsor's pediatric study plan (PSP) should contain comments on why patients between the ages of 0-2 will be excluded from the proposed trials.

**12. Regulatory and clinical:**

(b) (4)  
(u) (4)  
(b) (4) **Does FDA have any comment?**

Agency Response: *Information included in the Mechanism of Action section of the label should be adequately supported by nonclinical and clinical data. Labeling is a review issue requiring review of a submitted application; however it is unlikely that this proposal would be acceptable for label unless these changes were shown in the adequate and well controlled human trials. If you intend to include this information, the parameters noted above must be measured in humans.*

Meeting Comment: There was no discussion of this matter during the meeting.

**13. Regulatory: The Sponsor intends to submit an NDA on this product in eCTD format. Consistent with FDA's April 2009 guidance, the Sponsor plans to include the following summaries:**

**Module 2.5.4: Overview of Efficacy**

**Module 2.5.5: Overview of Safety**

**Module 2.7.3: Summary of Clinical Efficacy**

**Module 2.7.4: Summary of Clinical Safety**

**Module 5.3.5.3: Reports of Analyses of Data from more than one study:**

**-Integrated Summary of Effectiveness (ISE):**

**-Integrated Summary of Safety (ISS):**

**In the ISE, the Sponsor plans to present efficacy analyses of each pivotal clinical study (AR-13324-CS301 and AR-13324-CS302), and other relevant studies.**

**However, the Sponsor does not plan to conduct analyses in which studies are**

**combined.**

**In the ISS, the Sponsor plans to present an incidence table of adverse events in all studies in which humans (patients and healthy volunteers) were exposed to AR-13324 Ophthalmic Solution. The Sponsor plans to present an incidence table of adverse events from the two Phase 3 studies. With respect to the proposed package insert, the Sponsor intends to use the incidence of adverse events in the Phase 3 trials, as those representing the relevant long-term use.**

**Regarding electronic clinical data, the Sponsor is planning to use SDTM Version 1.3, Implementation Guide Version 3.1.3 and ADaM Version 2.1, Implementation Guide Version 1.0**

**Does FDA concur?**

*Agency Response: The proposal is acceptable; we would also expect summaries for Quality and Nonclinical. Final determination of the specific adverse event tables utilized in the labeling will be a review issue.*

*For the ISE, we recommend that you present analyses in which two Phase 3 studies are combined in addition to the separate analyses of each study.*

Meeting Discussion: The Sponsor proposed submitting SDTM - ADaM defined files only for the Phase 3 studies. The Agency stated this is acceptable as long as the Sponsor does not need the Phase 2 data to support approval. If so, they should submit the files for the Phase 2 data.

Additional Agency Comments:

*For the two Phase 3 trials only trial outlines are submitted, additional comments will be made once the final protocols are submitted.*

*Visual field (VF), pupil size, and cup to disc ratio (C/D) are recommended to be performed at baseline, months 3, 6, and 12. Visual Field (VF) using the same automated, threshold program for all evaluations. The line listings are recommended to include the average mean loss. A copy of all VF are recommended to be included in the case report forms. Pupil size is recommended to be recorded in 0.5 mm increments.*

*An evaluation of patient comfort after the administration of the drug product is recommended to be completed. If topically administered, dosing of drops should be at least 30 minutes after use of any anesthetic agent or IOP measurement.*

*Please be advised that a sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration (i.e., that triggers PREA) is required to submit an initial Pediatric Study Plan (PSP).*

*Under the Food and Drug Administration Safety and Innovation Act (FDASIA), a Pediatric Study Plan must be submitted within 60 days of an End-of-Phase 2 (EOP2) meeting.*

*The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:*

*<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).*

**ACTION ITEM:**

The Agency agreed to have an internal discussion of how the NDA would be affected if the b.i.d. arm shows superiority to the q.d. arm when only one clinical efficacy study is conducted.

**POST-MEETING ADDENDUM:**

During the April 11 meeting, the Sponsor raised questions about the proposed dosing regimen that Dr. Cox said the review team needed to discuss before responding to them. There was a follow-up telephone conversation with Dr. Albrecht and Dr. Cox on 4/22/14. During the call, Dr. Cox suggested Aerie submit their follow-up questions.

Following are Aerie's questions with the Agency's responses:

**Question 1. As discussed in the formal meeting, our intent was to apply for approval of our drug with q.d. dosing in the label, and our studies are designed to demonstrate that the drug is safe and effective under those conditions. Please help us understand the clinical/regulatory/legal basis for requiring a study of a different dosing regimen -- especially one that results in delivery of more drug to the patient-- than that for which we are seeking approval? We understand the standard for approving a drug is demonstrating safety and effectiveness to be evaluated "under the conditions of use prescribed, recommended or suggested in the proposed labeling" of the drug.**

*Agency Response: There is no legal requirement to study a different dosing regimen, however, the Agency generally recommends that more than one dosage regimen be studied during the development program.*

*If you choose to study only the q.d. dosing regimen (e.g., given q.h.s.), we recommend the control arm should also use a q.d. regimen, e.g., latanoprost ophthalmic solution or bimatoprost ophthalmic solution administered q.h.s., so the trial is double-masked. If you choose to study only the bid dosing regimen, we recommend that the control arm should also use a bid regimen, e.g., timolol ophthalmic solution administered bid so the trial is double-masked. If you choose to study both q.d. and b.i.d. dosing in the same study, you will also need to double-mask the trial, which may mean you will need to add a vehicle dosing regimen to one or more of the arms to*

*maintain masking and any or all of the following control arms may be acceptable: latanoprost ophthalmic solution administered q.h.s., bimatoprost ophthalmic solution administered q.h.s. or timolol ophthalmic solution administered b.i.d.*

**Question 2. As discussed at the formal meeting, if we design one of the efficacy trials to include a b.i.d. arm,** (b) (4)

Agency Response: (b) (4)

(b) (4)

**Question 3.** (b) (4)

(b) (4)

Agency Response:

(b) (4)

(b) (4)

**Question 4.**

(b) (4)

Agency Response: See response to Question 3.

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

/s/  
-----

WILEY A CHAMBERS  
05/14/2014



IND 113064

**MEETING MINUTES**

Aerie Pharmaceuticals Inc.  
Attention: Brian Levy, O.D, Chief Medical Officer  
135 Route 206  
Suite 15  
Bedminster, NJ 07921

Dear Dr. Levy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AR-13324 Ophthalmic Solution.

We also refer to the meeting between representatives of your firm and the FDA on March 10, 2014. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Controls activities leading to the Phase 3 program and the submission of a New Drug Application for AR-13324 Ophthalmic Solution.

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 questions, call me, at 240-402-3815.

Sincerely,

*{See appended electronic signature page}*

Navi Bhandari, Pharm.D  
Regulatory Health Project Manager  
Office of Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** EOP2

**Meeting Date and Time:** March 10, 2014 1:00 – 2:00 pm, EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** IND 113064  
**Product Name:** AR-13324 Ophthalmic Solution  
**Indication:** Treatment of elevated ocular pressure  
**Sponsor/Applicant Name:** Aerie Pharmaceuticals Inc.

**Meeting Chair:** Rapti D. Madurawe, Ph.D.  
**Meeting Recorder:** Navdeep Bhandari, Pharm.D.

**FDA ATTENDEES**

Rapti D. Madurawe, Ph.D.	Branch Chief
Bala Shanmugam, Ph.D.	CMC Lead
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager
Denise Miller	Quality Microbiology Reviewer
Andrew McDougal, Ph.D.	Pharmacology Reviewer
Wiley Chambers, M.D.	Supervisory Medical Officer
William Boyd, M.D.	Clinical Team Leader
Renata Albrecht, M.D.	Supervisory Medical Officer

**SPONSOR ATTENDEES**

Thomas Mitro	Chief Operating Officer
Brian Levy, O.D., M.S.	Chief Medical Officer
Casey Kopczynski, Ph.D.	Chief Scientific Officer
Ramesh Krishnamoorthy, Ph.D.	VP, Manufacturing
Mitchell A. DeLong, Ph.D.	VP, Chemistry
(b) (4)	(b) (4) (Consultant)
(b) (4)	(b) (4) (Consultant)
Marvin J. Garrett	Vice President
(b) (4)	Consultant

## 1.0 BACKGROUND

A Type B meeting briefing package was submitted February 6, 2014, for a March 10, 2014, End-of-Phase 2 CMC Meeting for AR-13324 Ophthalmic Solution (IND 113064).

## 2.0 DISCUSSION

This meeting's focus was to provide proposed plans for CMC topics relative to this IND, and gain input from the Agency on Aerie Pharmaceuticals Inc.'s plans for CMC topics for Phase 3 and the eventual NDA.

The Agency sent preliminary responses on March 6, 2014 to the Sponsor. The Sponsor asked to focus on questions 2, 5, 7, 9, 10, 11 and 12.

## 3.0 Questions

### Degradant Specification:

#### 1.

**1a. Does the Agency agree that the (b) (4) proposed which is being used for Phase 3 manufacturing is suitable for manufacturing drug substance registration and validation batches?**

#### Agency Response:

The proposed (b) (4) appears reasonable for the planned Phase 3 studies. Please see response to question 1b.

**1b. Are the proposed starting materials and controls in place for the Phase 3 (b) (4) deemed suitable and adequate for this phase of development?**

#### Agency Response:

We agree with the designation of (b) (4) as starting materials. (b) (4) used in the formation of the dimesylate salt does not meet the general principles for a starting material as it is not incorporated as a significant structural fragment into the structure of the drug substance. Please refer to ICH Q11. As outlined in the submission, the use of GMP grade (b) (4) with adequate controls for the different (b) (4) is reasonable. All batches should be continued to be monitored for the three potential (b) (4) in the API as committed in the submission.

*The specification proposed for the starting materials includes tests for the critical attributes to assure control of their quality. However, to ensure better understanding of the potential interactions among impurities from different starting materials, we recommend that you conduct studies to establish the fate of the impurities and to determine if any of the impurities are carried over to the API. Additionally, you should provide in the NDA a discussion on how the manufacturing process will purge the impurities. The NDA should provide COAs for the starting materials used in the manufacture of the API batches used for manufacturing the clinical trial material.*

**Discussion:** There was no specific discussion on this question.

2. Does the Agency agree that no new safety studies are required to specifically qualify the impurity profile of API produced from the proposed [REDACTED]<sup>(b) (4)</sup> for Phase 3 studies?

**Agency Response:**

*FDA concurs with this general approach. Please be aware that the adequacy of the ongoing 9-month GLP monkey toxicology study and the 6-month GLP rabbit toxicology study will be review issues, when the reports are received. Please submit the reports for these long-term studies prior to dosing patients longer than supported by the previously-submitted nonclinical studies (i.e. 28 days).*

*It is recommended that ocular tissue distribution be evaluated prior to the initiation of Phase 3 trials.*

*Please be aware that the proposed threshold of toxicologic concern (TTC) approach outlined in the meeting package is not applicable to [REDACTED]<sup>(b) (4)</sup>. These would be [REDACTED]<sup>(b) (4)</sup> compounds under the draft ICH M7 guidance<sup>1</sup>. For the NDA submission, propose compound-specific acceptable limits based on the available carcinogenicity data.*

**Discussion:** The Sponsor asked for clarification on the TTC approach for setting specifications. The Agency responded that the draft ICHM7 may be helpful for Aerie, and that future revisions may have more information. Approaches other than

---

<sup>1</sup> ICH M7. 2013. Draft consensus guideline. Current Step 2 version. Assessment and control of DNA reactive (mutagenic) impurities in pharmaceutical to limit potential carcinogenic risk. Accessible via: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm347725.pdf> and [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Multidisciplinary/M7/M7\\_Step\\_2.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_2.pdf)

those described in the draft may be acceptable. FDA noted that several papers in the published literature reported high carcinogenic potency for (b) (4) such that the default approach using TTC may not be scientifically justified. The Sponsor proposed using regulatory exposure limits for (b) (4) as a starting point, and estimating acceptable exposures based on comparative chemical activity. FDA concurred with this general approach. For the NDA, the acceptability of the specifications for (b) (4) will be a review issue.

### **Drug Substance Specifications and Registration Stability**

3. Does the Agency agree that the current controls in place for monitoring of (b) (4) in the API are sufficient?

**Agency Response:**

*The NDA should provide details on the validated method used for monitoring the (b) (4). We recommend that the levels continue to be monitored to demonstrate that (b) (4) are not formed on storage of the API.*

**Discussion:** There was no specific discussion on this question.

4. Does the Agency agree with the proposed storage and stability plan?

**Agency Response:**

*Stability plans appear to be reasonable, but we do recommend testing samples at both long-term and accelerated condition for all attributes and not as optional testing as proposed. In addition to the (b) (4) property, storage of the API in (b) (4) suggests that it could be (b) (4), but the briefing package makes no mention of any (b) (4) studies conducted. The NDA should provide data on (b) (4) and stress studies per ICH recommendation. The cumulative data package may then be used to justify the proposed specification (applicable over shelf-life) submitted in the NDA.*

**Discussion:** There was no specific discussion on this question.

5. Does the Agency agree that the specifications proposed for drug substance are appropriate for the current phase of development (Phase 3)? (NDA specifications will comply with the requirements proposed in ICH Q3A(R2))

**Agency Response:**

*The proposed specification appears reasonable for the planned Phase 3, but as you have indicated, the specification in the NDA should comply with ICH recommendations. Furthermore, depending on the data from the Phase 3 material, additional quality tests may be required. Regarding stereoisomerism, Table 7 in the submission indicates that at least (b) (4). Please comment on the stereoisomeric composition of the API used in other nonclinical and clinical studies.*

**Discussion:** The Sponsor indicated that they would follow ICH protocols as recommended in the preliminary comments sent by the Agency. The Sponsor stated that they are able to control the (b) (4) of the drug substance at (b) (4)%. The Sponsor indicated that the (b) (4) was intentionally spiked at (b) (4)% and that the (b) (4) was controlled at (b) (4)%. The clarification provided was acceptable to the Agency. The Agency requested that the Sponsor provide this information and justification in the NDA to which the sponsor agreed.

### **Drug Substance Manufacturing Plans**

6. In response to Aerie's initial IND filing, FDA specifically asked the Sponsor to submit a proposed (b) (4) plan for (b) (4). Does the FDA consider the submitted (b) (4) identification plan appropriate for the (b) (4) starting material used in the synthesis of the API?

**Agency Response:**

*The proposed plan appears reasonable. The controls presented in Table 19 should be reflective of the specification proposed in Table 5. Details on incoming acceptance material, (b) (4) and COA for the batch(es) used in the manufacture of the API should be provided in the NDA. Also, please refer to our response to question 1 on fate/purging of impurities from the starting materials.*

**Discussion:** There was no specific discussion on this question.

7. Does the Agency agree with Aerie's proposal to submit comparability protocols for alternative drug substance manufacturing site(s) and for alternate sources of Starting Materials as well as supportive stability studies to the IND?

**Agency Response:**

*The intent of your question is not clear. A comparability protocol may be submitted to the NDA, either at the time of NDA submission or after NDA approval. A comparability protocol to the IND is generally not recommended as the manufacturing process during*

*the IND stage is still under development and may undergo multiple changes before the final commercial manufacturing process is established.*

**Discussion:** The Sponsor indicated that they will file a comparability protocol in the NDA. The Sponsor plans to add an additional manufacturing site and an alternate supplier and inquired if there is a mechanism to discuss their plans with the FDA to receive feedback/input in the IND phase. The Agency responded that the Sponsor may request a meeting.

8.

**8a. Does the Agency agree that the proposed scale of API manufacturing for registration stability and validation batches is acceptable for NDA?**

**Agency Response:**

*Registration stability batches should be manufactured at commercial scale or at a minimum within pilot scale. Please refer to ICH Q1A(R2) for appropriate batch selection recommendations for drug substance and drug product registration stability batches. It is up to you to determine the appropriate commercial scale for your specific application.*

*Please refer to the Guidance for Industry, "Process Validation: General Principles and Practices" for recommendations on process validation.*

**8b. Does the Agency agree with Aerie's overall proposed manufacturing plan?**

**Agency Response:**

*The overall plan appears reasonable. In the NDA, please provide details including scale of manufacture, synthesis process used, intended purpose of the batch etc. to the batch analysis section.*

**Discussion:** There was no specific discussion on this question.

### **Drug Product Phase 3 Specifications**

9. Does the Agency agree that the specifications proposed for drug product (which will not include endotoxin limits) are appropriate for the current phase of drug development (Phase 3)? [NDA specifications will comply with the requirements proposed in ICH Q3B (R2)]?

**Agency Response:**

*The proposed specification is reasonable for the planned Phase 3 study. Adequacy of the drug product specification is an NDA review issue and upon evaluation of the data provided in the NDA, further tightening of the proposed acceptance limits and/or additional tests may be required for inclusion in the specification.*

*For an NDA, the plan for testing AET in the registration batches at release and in the stability program is not a recommended approach as it does not provide documentation of preservative effectiveness at the lowest acceptable preservative level in the product. The recommended approach would be to perform an AET study using the drug product formulated with the preservative at or below the lowest antimicrobial concentration based on the label claim. A good range would be 50% of the lowest acceptable preservative concentration. This study should be included in the NDA submission.*

**Discussion: The Sponsor asked for clarification on endotoxin testing, specifically if it was necessary from post Phase 3 or going into approval. The Agency responded that endotoxin testing not necessary for topical ocular products. The Sponsor agreed with the Agency about the comments regarding AET testing. The Sponsor is progressively monitoring for BEK only. The Sponsor asked that once they establish the lower limits if it was acceptable to not perform SET for registration and commercial batches. The Agency responded that the Sponsors request is acceptable.**

### **Drug Product Manufacturing and Stability Plans**

10.

**10a. Does the Agency agree that the proposed scale of Drug Product manufacturing for the registration stability and validation batches is acceptable for NDA submission and approval to support Aerie's planned commercial scale? Does the Agency agree with Aerie's overall proposed manufacturing plan?**

**Agency Response:**

*Please refer to the response to question 8a.*

*Adequacy of the manufacturing process will be evaluated during NDA review but the overall manufacturing plan is reasonable. Please note that manufacturing process for Phase 3 clinical trial material should represent the intended commercial manufacturing process. Any change to the Phase 3 clinical trial drug product formulation and/or manufacturing process may require additional studies to bridge the differences.*

**10b. Does the Agency agree that the amount of product to be filled in Aerie's proposed registration stability batches and sampling plan [REDACTED] (b) (4) [REDACTED] is acceptable?**

**Agency Response:**

Please clarify the purpose of the (b) (4) mL fill from the registration stability batches since you indicate that Phase 3 supplies will be manufactured on demand.

Sampling is a CGMP issue and the sampling plan is generally evaluated during inspection. In general, (b) (4) appears reasonable.

Please confirm that all (b) (4) fill volumes will be placed in the formal stability studies.

**Discussion:** The Sponsor indicated that they will be using the same formulation moving forward from Phase 3 to commercial. On the topic of (b) (4) Aerie stated that should a need for drug product arise during the Phase 3 trial, they will use part of the registration batches to fulfill the need. The Sponsor agreed to monitor and collect data on the stability batches and provide data to the Agency on all (b) (4) fill batches. The Sponsor clarified that the clinical batches are not (b) (4). In response to Agency's comment on ICH recommended batch size requirement of at least 2 pilot scale for stability batches, the Sponsor responded that they will comply with ICH recommendations with 2 batches at pilot scale.

**Drug Product Packaging Change and Stability Plans**

11.

11a. Does the Agency agree that the data from the registration stability and supporting stability batches are sufficient to demonstrate the equivalence of the formulation in the two fill sizes in their respective packaging configurations (i.e. commercial and professional samples)?

**Agency Response:**

The question about demonstrating equivalence of the formulations in the two fill size is not clear to us. The commercial formulation should be the same as the formulation in Phase 3 studies. All (b) (4) fill volumes you propose to use should be of identical formulation and be used in stability studies.

11b. Does the Agency agree that the registration and supportive stability data available at the time of NDA submission, along with a commitment to provide 18-month stability data at the long-term storage condition during the NDA review, would be supportive of a 24-month expiration date for the commercial and professional sample presentations?

**Agency Response:**

*The NDA at the time of submission has to provide adequate stability data (at least 12-month long-term and 6-months accelerated, per ICH Q1A(R2)) on all fill configurations for three registration batches to support the requested expiration date. Additional data submitted during NDA review may or may not be accepted.*

**Discussion:** The Sponsor states that the formulation composition will not change all the way to the commercial batch and that the only difference will be the size of the bottle. Additionally, the clinical batch will have a yellow cap. The Agency requested the Sponsor consider the differences in the headspace of the different containers in their stability studies and that the bottles be stored in different spatial orientations. The Sponsor agreed to provide data in different orientations in the NDA. The Agency requested that the Sponsor provide a comparison of drop volume from the various fill volume configurations. The Sponsor agreed to provide the requested volume size data. The Sponsor confirmed that they will provide 12 months of long term and 6 months of accelerated stability data. Since the dosing regimen has not been determined yet, the Agency reminded Aerie the stability data required from the various fill lots will depend on the commercial packaging configuration. Aerie acknowledged and mentioned that if a (b) (4) mL fill volume is required, they may consider marketing (b) (4) Aerie will update the Agency as a decision is made.

**Drug Product Leachables**

- 12. Does the Agency agree that the proposed design of the one-time leachables study of the drug product on stability is adequate to support NDA submission and approval?**

**Agency Response:**

*The overall approach to testing extractables and leachables is reasonable. However, we recommend that leachable study data adequate to support the expiration date be provided in the NDA at the time of submission. Also, the leachable study should use the proposed commercial formulation in the primary and secondary packaging system (including labels, inks, glues, etc.). We acknowledge that a larger surface area is being considered but as indicated in Table 52, the proposed commercial packaging also provides for (b) (4) which is not part of the packaging for the registration stability lots.*

*The current proposal to use a white cap is acceptable. If the cap color changes, additional leachable studies will be expected.*

**Discussion: The Sponsor confirmed that the current formulation will remain to be the commercial formulation. Since the primary and secondary packaging is representative of the commercial submissions, the sponsor asked if the Agency will consider a single set of information for both sizes. The Agency responded that the request is acceptable if there are no changes to the bottle, label or adhesive. The Sponsor acknowledged the Agency's response on the cap color and committed to provide the Agency with a side by side comparison of extractables once they know what cap color they will use. The Sponsor asked if the information they plan to submit is acceptable and the Agency responded that the request was acceptable if the Sponsor can demonstrate that that the data between the two different color caps are the same and, that the data will have to be reviewed to make a final determination.**

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

/s/  
-----

BALAJEE SHANMUGAM  
04/08/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 208254

**LATE-CYCLE MEETING MINUTES**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Vice President, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhopressa (netarsudil ophthalmic solution) 0.02%. We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 29, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Eithu Lwin, Regulatory Project Manager at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

William M. Boyd, MD  
Cross Discipline Team Leader  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** September 29, 2017, 10:00-11:00AM EST  
**Meeting Location:** Teleconference

**Application Number:** NDA 208254  
**Product Name:** Rhopressa (netarsudil ophthalmic solution) 0.02%  
**Applicant Name:** Aerie Pharmaceuticals, Inc.

**Meeting Chair:** William Boyd, Cross Discipline Team Leader (CDTL)  
**Meeting Recorder:** Eithu Lwin, Regulatory Health Project Manager

**FDA ATTENDEES**

John Farley, Deputy Director, Office of Antimicrobial Products  
Renata Albrecht, Division Director, Division of Transplant and Ophthalmology Products (DTOP)  
Wiley A. Chambers, Deputy Director, DTOP  
William M. Boyd, CDTL, DTOP  
Sonal Wadhwa, Clinical Reviewer, DTOP  
Rhea Lloyd, Clinical Reviewer, DTOP  
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP  
Aling Dong, Pharmacology/Toxicology Reviewer, DTOP  
Yan Wang, Statistical Team Leader, Office of Biostatistics (OB) / Division of Biometrics IV (DBIV)  
Yunfan Deng, Statistical Reviewer, OB/DBIV  
Chunchun Zhang, Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ) / Office of New Drug Product I (ONDPI)  
George Lunn, Product Quality Reviewer, OPQ/ONDPI  
Stephanie Villasis, Pharmacy Student Intern  
Eithu Lwin, Regulatory Project Manager, DTOP

**APPLICANT ATTENDEES**

Tom Mitro, President and Chief Operating Officer  
Theresa Heah, Vice President, Clinical Research and Medical Affairs  
Casey Kopczynski, Chief Scientific Officer  
Marvin Garrett, Vice President, Regulatory Affairs and Quality  
Cindy Martin, Vice President, Regulatory Affairs  
Kristine Erickson, Vice President, Clinical Research  
Ken Ruettimann, Vice President, Manufacturing  
George Baklayan, Director, Regulatory Affairs/Technical Writing  
Ted Wheeler, Director, Quality Assurance

(b) (4) Consultant, (b) (4)

## **BACKGROUND**

NDA 208254 was submitted and received on February 28, 2017, for Rhopressa (netarsudil ophthalmic solution) 0.02%.

Proposed indication(s): Reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension

PDUFA goal date: February 28, 2018

FDA issued a Background Package in preparation for this meeting on September 25, 2017.

## **DISCUSSION**

For the purposes of these minutes, the information that the CDTL presented are in normal font and the meeting discussions are in ***bold italics***.

### **1. Introductory Comments**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

***Discussion: None.***

### **2. Discussion of Substantive Review Issues**

No Discipline Review Letters have been issued to date.

No substantive review issues have been identified to date, other than those previously identified at the Mid-Cycle Meeting held on July, 25, 2017:

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.

- Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.

***Discussion:*** Applicant emphasized that they believe Rhopressa effectively lowered IOP at all levels of IOP and did not want to give the impression that Rhopressa was not able to lower IOP above a certain level of baseline IOP. The Division acknowledged the Applicant's position.

*The Division asked if the Applicant had prepared slides for the upcoming advisory committee meeting regarding the efficacy position stated above and asked if Applicant was willing to share these slides with the Division prior to the meeting. Applicant agreed to share presentation slides several days ahead of the advisory committee meeting.*

### 3. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee meeting is planned for Friday, October 13, 2017, FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503) 10903 New Hampshire Avenue, Silver Spring, Maryland.

***Discussion:*** Applicant inquired about the reasoning for (b) (4) in the Division's edits to the package insert. The Division responded that there is insufficient justification for including (b) (4) and that the Division is open to suggestion on considering these during the labeling review. The Division confirmed that as stated in the Filing letter and Mid-Cycle Communication, if major deficiencies are not identified during the review, the Division plan to communicate proposed labeling by November 24, 2017.

### 4. Review Plans

- No outstanding information requests.
- Quality Assessment and Facilities review is outstanding. Awaiting completion.

***Discussion:*** The Applicant inquired about the status of the pre-approval inspection. The Division responded that the Applicant would need to get the details directly from the contract manufacturer, and that the inspections are on track to be completed by the PDUFA goal date.

### 5. Wrap-up and Action Items

- Applicant will share their presentation slides several days ahead of the advisory committee meeting.
- The meeting minutes for this Late-Cycle Meeting will be issued within 30 days.
- This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/  
-----

WILEY A CHAMBERS

10/24/2017

Wiley Chambers, MD for William Boyd, MD



NDA 208254

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Aerie Pharmaceuticals, Inc.  
Attention: Cindy Martin  
Vice President, Regulatory Affairs  
2030 Main Street, Suite 1500  
Irvine, CA 92614

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhopressa (netarsudil ophthalmic solution) 0.02%.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 29, 2017. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Eithu Lwin, Regulatory Project Manager, at (301) 796-0728.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Transplant and Ophthalmology  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** September 29, 2017, 10:00-11:00AM EST  
**Meeting Location:** Teleconference

**Application Number:** NDA 208254  
**Product Name:** Rhopressa (netarsudil ophthalmic solution) 0.02%  
**Indication:** reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension  
**Applicant Name:** Aerie Pharmaceuticals Inc

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

#### 2. SUBSTANTIVE REVIEW ISSUES

No substantive review issues have been identified to date, other than those previously identified at the Mid-Cycle Meeting held on July, 25, 2017:

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.

- Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.

### **3. ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is planned for Friday, October 13, 2017, FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503) 10903 New Hampshire Avenue, Silver Spring, Maryland.

### **4. REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

### **LCM AGENDA**

1. Introductory Comments – 5 minutes William M. Boyd, M.D. (CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

#### Clinical

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.
  - Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.
3. Review Plans – 5 minutes
    - No outstanding information requests.
    - Quality Assessment and Facilities review is outstanding. Awaiting completion.
  4. Wrap-up and Action Items – 10 minutes

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

/s/  
-----

RENATA ALBRECHT  
09/25/2017