

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208135Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208135

SUPPL #

HFD #

Trade Name N/A

Generic Name Tetracaine Hydrochloride Ophthalmic Solution

Applicant Name Alcon Research, Ltd.

Approval Date, If Known February 29, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2) literature only

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

YES NO

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

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

c) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 21717

Pliaglis (lidocaine 7% and tetracaine 7%) cream

NDA# 21623

Synera (lidocaine 70mg and tetracaine 70mg) topical patch

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

This is a 505(b)(2) literature only NDA application

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

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

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
<i>*Only literature references, no clinical investigations conducted by the applicant</i>		
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
<i>*Only literature references, no clinical investigations conducted by the applicant</i>		
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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

No new investigations were submitted. This is a 505(b)(2) literature only application

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

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

Investigation #1 ***No clinical investigations conducted by applicant***

IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

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

Investigation #1 *No clinical investigations conducted by applicant*

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
! NO
! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Eithu Z. Lwin, PharmD
Title: Regulatory Health Project Manager
Date: February 23, 2016

Name of Office/Division Director signing form: Renata Albrecht, MD
Title: Director, Division of Transplant and Ophthalmology Products

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

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/s/

EI THU Z LWIN
02/29/2016
NDA 208135 exclusivity summary

RENATA ALBRECHT
02/29/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 4, 2016 at 2:00 PM (EST)
February 19, 2016 at 1:00 PM (EST)
February 22, 2016 at 2:00 PM (EST)

Application Number: NDA 208135
Product Name: tetracaine hydrochloride ophthalmic solution, 0.5%
Indication: Procedures for which a rapid ad short acting topical ophthalmic anesthetic is indicated
Applicant Name: Alcon Research, Ltd.

FDA Participants

2/4/2016 teleconference:

Renata Albrecht, Division Director
Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Leader
Anamitro Banerjee, Product Quality Team Leader
Milton Sloan, Product Quality Reviewer
Aaron Ruhland, Pharm/Tox Reviewer
Eithu Z. Lwin, Regulatory Health Project Manager

2/19/2016 teleconference:

Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Leader
Eithu Z. Lwin, Regulatory Health Project Manager

2/22/2016 teleconference:

Renata Albrecht, Division Director
Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Leader
Jin Chen, Associate Director for Labeling
Balajee Shanmugam, Product Quality Branch Chief
Anamitro Banerjee, Product Quality Team Leader
Milton Sloan, Product Quality Reviewer
Abel Eshete, Statistical Reviewer
Eithu Z. Lwin, Regulatory Health Project Manager

Applicant Participants

2/4/2016 teleconference:

James Wheeler, Project Head
Michela Montecchi-Palmer, Clinical Lead
Joseph Bocclair, Pharmaceutical Development
Kevin Nugent, Regulatory Change Control
Teresa McElvaney, Technical (CMC) Regulatory Affairs
Barry Astroff, Toxicology

Thomas Valencia, Medical Safety
Craig Salem, Medical Safety
Paul Nitschmann, Regulatory Affairs

2/19/2016 teleconference:

James Wheeler, Project Head
Paul Nitschmann, Regulatory Affairs

2/22/2016 teleconference:

James Wheeler, Project Head
Michela Montecchi-Palmer, Clinical
Thomas Valencia, Medical Safety
Barry Astroff, Preclinical
Jwalitha Shankardas, Global Labeling
Paul Nitschmann, Regulatory Affairs

BACKGROUND:

The Division arranged three teleconferences for February 4, 19, and 22, 2016, to discuss issues identified during the review of NDA 208135.

DISCUSSION:

2/4/2016 teleconference:

The Division issued written information request on February 3, 2016.

- Item a of the IR: Alcon went over their manufacturing history that was emailed to the FDA RPM on 2/2/16. The Division inquired why Alcon sterilize the U.S. product and Alcon replied the exterior of the bottle and the label are sterilized since the bottles are going into a sterile field. The Division inquired regarding the oldest product Alcon has on stability and Alcon replied they generally only keep their products for shelf-life, approximately (b)(4) months. The Division inquired if there is information on levels of (b)(4) and Alcon stated they do not have quantitative value on (b)(4). FDA asked Alcon to test for (b)(4) level of product near expiration date or past expiration date. Alcon looked into their inventory and found products that are (b)(4) months past expiration and stated they will provide the data by the end of next week. The Division stated CMC team will review the information that Alcon emailed on 2/2/16, and will provide additional questions, if any, by next week.
- Item b of the IR: Regarding exposure, Alcon stated prescriptions are not written for the product and provided the Division with the number of units sold in the U.S. (i.e. approximately (b)(4) units per year). Alcon stated that it estimates that Alcon's tetracaine constitutes approximately 30-50% of the use of topical anesthetics.
- Item c of the IR: The Division requested for history of tetracaine Steri-Unit adverse effects. Alcon stated they have submitted in the NDA all history of tetracaine adverse effects and not

just Steri-Unit. Alcon stated there are 86 post-market adverse events for tetracine Steri-Unit and agreed to submit all 86 of the individual med-watch forms.

2/19/2016 teleconference:

The Division noted that the nonclinical portion of the NDA references the Agency's review of another application, which was not Alcon's intent, and recommended the following 3 options.

1. Remove this reference and any information derived from this reference
2. Obtain right of reference to that study
3. Amend 505(b)(2) indicating that Alcon is taking information from the label of another application

Alcon stated that they did not intend to rely on any other application and will provide updated labeling by Monday, February 22, 2016.

The Division went over Alcon's revised package insert and provided additional recommendations.

2/22/2016 teleconference:

The applicant stated they will be submitting through the Gateway four (4) artworks of the carton and container labels, revised 3.2.P.5.1 Specification, updated package insert, and updated toxicology NDA sections in line with package insert. The Division requested that the applicant submit the full stability report. The applicant agreed to work with their chemistry team in getting the stability report submitted.

The Division stated the new Pharm/Tox reference titled, (b) (4) (b) (4), that the applicant emailed earlier on February 22, 2016, is a summary report and since it does not contain raw data, it cannot be used to support labeling. The Division recommended additional revisions to the package insert.

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/s/

EI THU Z LWIN
02/29/2016
NDA 208135 memo of tcon



NDA 208135

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D.
Title: Head, Regulatory Affairs Pharma
6201 South Freeway, Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr Nitschmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tetracaine Hydrochloride Ophthalmic solution, 0.5%.

We will be performing methods verification studies on Tetracaine Hydrochloride Ophthalmic solution, 0.5%, as described in NDA 208135.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

PROC-0005269: HPLC Assay Analysis of Tetracaine HCl and Related Impurities in Drug Substance and Selected Ophthalmic Solutions

Samples and Reference Standards

[Redacted] (b) (4)

No less than 4 (separate) 4-mL STERI-UNIT packages

Equipment

[Redacted] (b) (4)

Please include the (M)SDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this letter. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Digitally signed by Michael E. Hadwiger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300384000,
cn=Michael E. Hadwiger -S
Date: 2016.02.26 15:12:49 -06'00'

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

**PeRC Meeting Minutes
January 20, 2016**

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Linda Lewis
Thomas Smith
Daiva Shetty
Gettie Audain
Meshaun Payne
Dianne Murphy
Adrienne Hornatko-Munoz
Michelle Roth-Kline NON-RESPONSIVE)
Rosemary Addy
Wiley Chambers
Shrikant Pagay
Lili Mulugeta
Freda Cooner
Peter Starke
Dionna Greene
Barbara Buch
Rachel Witten
Colleen Locicero

Agenda

9:00	NON-RESPONSIVE				
9:10					
9:20					
10:20					
10:45					
11:00					
11:10	NDA 208135	Tetracaine Hydrochloride Ophthalmic Solution (Assessment)	DTOP	Ei Thu Lwin	For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated
11:20	NON-RESPONSIVE				
11:30					
11:40					
11:50					
12:00					

NON-RESPONSIVE

Tetracaine Hydrochloride Ophthalmic Solution (Assessment)

- Proposed Indication: For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated.
- This product triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, route of administration and has a PDUFA goal date of February 29, 2016
- The division noted that the product was previously a marketed unapproved product where the sponsor was requested to submit a marketing application based on literature only.
- The assessment is based published literature (including adequate and well-controlled trials) in pediatric patients as well as uncontrolled data on use of tetracaine as a topical ocular anesthetic in infants with retinopathy of prematurity.

- *PeRC Recommendations:*
 - The PeRC agreed with the division's full pediatric assessment for this product. There were no specific safety concerns identified in pediatric patients.

NON-RESPONSIVE

5 Pages have been Withheld in Full as NON-RESPONSIVE immediately following this page

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/s/

MESHAUN L PAYNE
02/04/2016



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

COMMUNICATION SHEET

DATE: February 3, 2016

To: Paul Nitschmann, MD Head, Regulatory Affairs Pharma	From: Eithu Z. Lwin, PharmD Regulatory Project Manager
Company: Alcon Research, Ltd.	Division of Transplant and Ophthalmology Products
E-mail: paul.nitschmann@alcon.com	E-mail: Eithu.Lwin@fda.hhs.gov
Phone Number: 806-759-3584	Phone Number: 301-796-0728

Subject: Find enclosed comments on NDA 208135

Total no. of pages including cover: 4

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 208135
Tetracaine Hydrochloride Ophthalmic Solution, 0.5%
Paul Nitschmann, MD

Dear Dr. Nitschmann,

We are continuing the review of your NDA 208135, including assessment of the (b) (4) (b) (4) whose levels are above the qualification threshold described in the ICH Q3B(R2) Guideline for Impurities in New Drug Products. We requested historic results of impurity testing and you stated that impurity testing was not historically performed. We also acknowledge that you have stated “Alcon confirms that the process proposed in the NDA is identical to the process used to manufacture the currently marketed product. Alcon reviewed the change control history for the last 10 years and confirms there have been no changes to the process for the currently marketed product over that time period. The last major change to the process was in 1996 with the move of manufacture (and associated changes) to another building on the Alcon Fort Worth campus.”

Your statement would imply that because the manufacturing process has not changed, the level of these impurities has been historically present in the product and this product had been administered to patients since 1996. In other words, there is almost two decades of clinical use of the product with these levels of impurities and presumably no clinically significant impurity-related toxicity has been reported. To support your statements about manufacturing, please respond to item a. below, and to address the utilization and adverse event reporting, please respond to item b. and c.

- a. Provide a comparison of the manufacturing process for the currently marketed drug product since the last major change (indicating the date) and the process proposed in the NDA. Highlight the changes and their potential impact on the drug product quality.
- b. You state that Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT® is a sterile, preservative-free formulation of tetracaine, currently marketed in the U.S. by Alcon, Inc., and is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. Provide the extent of patient use of your product annually (number of vials or other approximation) over the past 10-20 years, including what percentage of patients receiving tetracaine HCl 0.5% are given the Alcon product
- c. Provide information on the toxicity anticipated from the unqualified impurities (if any) and post-marketing adverse event reporting for your product in the last two decades.

Alternatively, conduct an appropriate nonclinical study to qualify these two impurities.

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

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/s/

EI THU Z LWIN
02/03/2016
NDA 208135 IR



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. **We request a prompt written response by January 15, 2016, in order to continue our evaluation of your NDA.**

A. We request the following information:

1. Provide an updated FDA Form 356h that includes the contract testing laboratory that currently supports your [REDACTED] (b) (4) testing for NDA 208135.

If you have any questions, call Erin Andrews, Regulatory Business Process Manager, at (240) 402-8578.

Sincerely,

Erin Andrews -A

Digitally signed by Erin Andrews -A
DN: cn=US, ou=US Government, ou=HHS, ou=FDA,
ou=People, cn=Erin Andrews -A,
0.9.2342.15200306.100.1.1=2001366614
Date: 2016.01.14 11:23:42 -0500

Erin Andrews, Pharm.D. USPHS
Regulatory Health Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research Branch



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. **We request a prompt written response by January 15, 2016, in order to continue our evaluation of your NDA.**

Drug Product

1. Please indicate where full information on the components and composition of the container label, adhesive, label coating, and inks is located in the NDA. You have indicated use of a (b) (4) label with (b) (4) adhesive as components and indicate in Table 2.3.P.7-1 the supplier and/or DMF information not applicable.
2. Please indicate if the components and composition information of the immediate container label meets requirements of FDA 21 CFR.175.105, 21 CFR.176 and 21 CFR.177.
3. Please also indicate that the affixed label supplier and proposed marketed components used in the leachable /extractable studies (Alcon Technical Report TDOC-0018674) is reconciled.
4. The 0.5% strength is calculated based on amount of tetracaine hydrochloride. For consistency with FDA's guidance on "Naming of Drug Products Containing Salt Drug Substances" and the USP Salt Policy, please propose an equivalent statement for label, e.g.: *Tetracaine hydrochloride (0.5%) equivalent to tetracaine (0.44%).

If you have any questions, call Erin Andrews, Regulatory Business Process Manager, at (240) 402-8578.

Sincerely,

Erin Andrews

-A

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

Digitally signed by Erin Andrews -A
DN: c=US, ou=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Erin Andrews -A,
0.9.2342.19200300.1001.1-2001366614
Date: 2016.01.11 15:45:38 -0500



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. **We request a prompt written response by January 04, 2016, in order to continue our evaluation of your NDA.**

Microbiology

1. In the 11/13/15 Amendment (response to question 13b), it is acknowledged that seal integrity testing is performed by visual inspection. A link to the executed batch record for Lot 228721F is provided for acceptance criteria (11/13/15, 3.2.R, executed-batch-record.pdf, p. 138 of 202); however, the acceptance criteria are not readily apparent. Please provide the test method and acceptance criteria for the seal integrity leak test to be performed on (b)(4) blister packs.
2. With regard to product release specifications, analytical methods, and method validation:
 - a. In the 11/13/15 Amendment (response to question 19), it is acknowledged that the Regulatory Specifications for the subject drug product in 3.2.P.5.1 has been revised to include the test for "Sterility, Exteriors" in addition to the test "Sterility". However, it is also noted that the footnote 'd' to Table 3.2.P.5.1-1 no longer includes the last sentence that was previously added in the 07/15/15 submission for clarification: "Sterility testing will also be performed at expiry for any commercial lots placed on sterility." For clarity, please provide a revised Table 3.2.P.5.1-1 that addresses whether sterility testing (either for contents and/or exteriors) is to be performed at expiry for commercial lots and that clarifies that the test for "Sterility" is a test for "Sterility, Contents."
 - b. It is noted that the test method for "Sterility, Exteriors" is not provided in 3.2.P.5.2 and that the method validation is not provided in 3.2.P.5.3. Please provide the test method and corresponding test method validation.
3. With regard to shelf-life specifications and the post-approval stability protocol and commitment, it is not clear whether the test "Sterility, Exteriors" will be performed at expiry for commercial stability lots added to the stability program post-approval (11/13/15 Amendment, 3.2.P.5.1, page 1 of 1, and 07/15/15 Amendment, 3.2.P.8.2, page 1 of 2). Please provide a revised Post-Approval

Stability Protocol and Commitment that clarifies the microbiological tests that will be performed for commercial lots placed on stability post-approval and the testing intervals.

Process

4. With regard to (b) (4) in Tetracaine HCl in 4 mL MDPE Droptainers™, Table 4, in your Validation summary (Section 3.2.P.3.5.3-7) includes test results.
 - a. Provide the analytical methods and method validation report for (b) (4).
 - b. Include a summary of (b) (4) available from recent batches of your commercially marketed drug product.
 - c. Please provide your acceptance criteria for limits of (b) (4) with empirical safety data to support the proposed limits. Alternately, revise your limits to those supported by safety data available in the public domain.
5. We acknowledge that your Amendment (response to IR Issue 2, Seq 0006, received 12/02/2015), includes a test for assay of bulk solution or filled unit samples; however it states that the test is to be performed (b) (4). Revised Section 3.2.P.3.4., does include in-process test for Tetracaine assay with acceptance limits, but does not specify the test sample. Please clarify.
6. Tabulate your commercial acceptance limits for reconciliation for each phase of your process (b) (4) and incorporate the acceptance limit ranges into your batch production and packaging records.

Drug Product

7. The acceptance criterion of NMT (b) (4)% at release and shelf life for (b) (4) impurities in the drug product specification is not supported by the batch analysis and stability data. Please tighten the acceptance criterion to NMT (b) (4)% release and shelf life. Although a value of (b) (4)% is predicted based on the one sided 95% confidence interval from statistical analyses, our recommendation is based on release and stability data provided that show up to (b) (4)% for accelerated and (b) (4)% long term (104weeks).
8. The acceptance criterion of NMT (b) (4)% at release and shelf life for total impurities in the drug product specification is not supported by the batch analysis and stability data. Please tighten the acceptance criterion to NMT (b) (4)% release and shelf life. Although your statistical analyses predicts a range from (b) (4)% based on the upper 95% confidence limit, our recommendation is based on release and stability data provided. These data show upper limits ranges up to (b) (4)% for accelerated and (b) (4)% long term; (b) (4)% (104 weeks).

If you have any questions, call Erin Andrews, Regulatory Business Process Manager, at (240) 402-8578.

Sincerely,

Erin Andrews -A

Digitally signed by Erin Andrews -A
DN: cn=US, ou=US Government, ou=HHS,
ou=FDA, ou=RegAff, cn=Erin Andrews -A,
0.9.2342.19200310.100.1.1=2001966614
Date: 2015.12.20 16:24:30 -05'00'

Erin Andrews, Pharm.D. USPHS
Regulatory Health Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research Branch



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests.

We request a prompt written response by **December 2, 2015**, in order to continue our evaluation of your NDA.

1. In your amendment dated November 13, 2015, you have indicated that the proposed drug product presentation and manufacturing process are the same as those of the historically marketed commercial product. Provide analytical results from impurity testing of multiple lots of your historically marketed product to support the proposed drug product impurity specifications.
2. With regards to Issue #6, based on information provided, your reference to previously submitted bundled CBE supplement (approved on March 30th, 2015) to remove chemical assays from in-process testing does not appear to be relevant as it does not cite specific NDA's covered and does not specify that the Tetracaine Hydrochloride ophthalmic solution product was included. Your proposal to eliminate in-process test for assay of bulk solution is not acceptable as there continue to be changes to the assay over the subsequent (b) (4). Therefore, continue to include in-process testing for assay of bulk solution or of filled unit samples subsequent to (b) (4) for each batch to sufficiently capture the variability and ensure adequate control.

If you have any questions, call Erin Andrews, Regulatory Business Process Manager, at (240) 402-8578.

Sincerely,

Erin Andrews -

A

LT, Erin Andrews, PharmD
Regulatory Business Process Manager (RBPM)
Office of Program and Regulatory Operations
Center for Drug Evaluation and Research Branch

Digitally signed by Erin Andrews -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Erin Andrews -A,
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Date: 2015.11.24 13:13:39 -05'00'



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by November 15, 2015, in order to continue our evaluation of your NDA.

1. Provide a comparison of your proposed drug product presentation with your historically marketed commercial product with regards to
 - a. Formulation, manufacturing process, including key process parameters and controls for (b) (4) sterilization of blister packs
 - b. Container closure system including type, fill volume, and materials of construction
 - c. Release and stability specifications, including tetracaine assay and impurities. Also include representative results of batch release and stability testing for your marketed product demonstrating that the impurities at the proposed levels are present in commercial circulation.

Drug Product Manufacturing Process:

2. Your description of the manufacturing process indicates that each labeled bottle is sealed in a polyvinylidene chloride (PVC) blister with TYVEK® backing material which provides tamper evidence. Upon review of the provided blank master batch record, the reviewer could not locate sections related to blister packaging. The Executed Batch Record for primary stability Lot No. 228418F did not include blister packaging information; Fort Worth Blister Lot No. 228721F is referenced for this stability lot. Please direct the reviewer to appropriate sections of batch record or provide adequate description of the blister packaging operations, equipment and controls to support your submission.

3. Provide the in-process testing results for the three primary stability batches listed in Table 3.2.P.5.4-1. Provide a summary of the in-process tests, test methods, and test results supporting these batches.
4. Clarify the units of measure '(b) (4)' used for Tetracaine HCl, USP (Page 13 of 137, Step 5.8) and '(b) (4)' used for Water for Injection (b) (4)
5. The (b) (4) validation study report (Exhibit 3.2.P.3.5.3-7, (b) (4) Blister Packed Product) uses a half cycle test with exposure dwell of (b) (4) minutes to validate sterilization and uses a full cycle test with exposure dwell of (b) (4) minutes and an aeration cycle of NLT (b) (4) days to establish no deleterious effects of (b) (4) and acceptable residual levels. Provide results for Tetracaine impurities observed in 4 mL round MDPE containers after each full cycle test (supporting the information provided in Table 5) and half cycle validation study (supporting the information provided in Table 6).
6. In process tests conducted on the post (b) (4) sample (b) (4) are not listed. List tests and acceptance criteria including bulk (b) (4) solution assay with acceptance limits, if not already being conducted.
7. A fill of 4mL is reported for the drug product, however, there are no weight or volume ranges provided for the filling operation. Provide fill weight ranges for each filling line, and specify the frequency of testing of fill weight and torque measurements in your in-process controls.
8. Tabulate your current acceptance limits for yield and reconciliation for each process step (b) (4). Provide a summary of yield and reconciliation results for each process step for your 3 primary stability batches.

Drug Product:

9. You report a target fill and label claim of (b) (4) mL as part of the product packaging specifications in section 7 of TDOC-0017080 provided in 3.2.P.3.3 of the NDA. Please clarify inconsistency.
10. You have provided a report that indicates using a (b) (4) mL container closure system for USP toxicological and leachable testing of the components. Also provided are references to component material resins. Please provide the qualified supplier (or list of suppliers) with actual acceptance criteria and CoAs for the proposed bottle, dispensing plug, closure, label, blister, and backing for the container closure system.
11. Please provide details of the container closure label, adhesive, printing ink used and leachable profile. Also provide information on the leachables studies conducted for the label components and the list of any potential leachables and the concentration observed.

Microbiology:

12. With regard to the primary container/closure system integrity testing (3.2.P.2.5, Appendix 2, 32p25-app2-032-38540-0598.pdf), please state if the (b) (4) mL blended bottles and (b) (4) mm flat tip LDPE dropper tips/plugs used in the container/closure integrity test challenge study have the same bottle neck and plug dimensions, and the same thread diameter or thread spacing as the (b) (4) bottles and plugs proposed for the subject drug product. If not, please provide

container/closure integrity test data from a study utilizing either the same or an equivalent container/closure system as proposed for the drug product.

13. With regard to the secondary packaging, namely the PVC blister with heat sealed Tyvek backing, it is understood that sterility of the interior of the sealed package and on the exterior surfaces of the primary container/closure system is assured by validation of the blister pack (b) (4) process provided in Exhibit 3.2.P.3.5.3-7. Please address the following:
 - a. Provide validation that demonstrates that the blister packs (b) (4) function as a barrier to microbial ingress. Please include a description of the method, materials, controls, and acceptance criteria.
 - b. Describe any seal integrity testing performed and acceptance criteria.
 - c. Address how sterility is maintained over the shelf-life.
14. With regard to environmental monitoring and bioburden testing of WFI, bulk drug solution, and packaging components:
 - a. Provide the growth media used for the environmental monitoring testing of air, surface, and personnel samples.
 - b. Describe the actions taken when levels are exceeded for WFI microbiological monitoring. Please address both bioburden and bacterial endotoxins testing.
 - c. Describe the actions taken when levels are exceeded for bulk drug solution bioburden testing. It is understood that the predominant contaminant is identified. Please comment on any other actions taken.
 - d. Apart from periodic bioburden testing performed for (b) (4) packaging components, please describe any bioburden testing of other packaging components that is performed prior to sterilization. Also, please provide the corresponding acceptance criteria.
15. With regard to the (b) (4) of the subject drug product, describe the integrity test method(s) that will be used pre- and post-use and include the acceptance criteria.
16. With regard to the requalification of (b) (4) sterilization of processing equipment, address the following:
 - a. Describe the microbiological methods for BIs including growth media and incubation time and temperature.
 - b. For the reported requalification studies, two of the studies appear to be performed in 2015. Please clarify the dates, and if any were performed in 2015, then please provide a full description of the BIs used (i.e., carrier, manufacturer, lot number, expiry, population, confirmed count, and D value).
17. With regard to the requalification of (b) (4), please address the following:

- a. Please describe the microbiological methods for BIs including growth media and incubation time and temperature.
 - b. For the reported requalification studies, please clarify the acceptance criteria and comment on whether BI positive controls were performed.
18. With regard to the validation for [REDACTED] (b) (4) blister packs, please address the following:
- a. For the half cycle and full cycle studies reported in Tables 2 and 3 (Exhibit 3.2.P.3.5.3-7), please provide the dates the studies were performed.
 - b. It is noted that the configuration for a maximum load is provided (Exhibit 3.2.P.3.5.3-7, page 8 of 14), but no corresponding minimum load is described. Please provide a description of the minimum load. Also, please clarify if the load(s) used in the reported validation studies are the same as those proposed for commercial production.
 - c. Please describe the microbiological methods for BIs including growth media and incubation time and temperature.
 - d. For the reported requalification studies (2012), please provide a full description of the BIs used (i.e., carrier, manufacturer, lot number, expiry, population, confirmed count, and D value).
 - e. For the reported requalification studies (2012-2014), please clarify the loading pattern(s) and container/closure system(s) used. The number of BIs used (PCDs and tubing packs) implies different load sizes than the initial studies (Exhibit 3.2.P.3.5.3-7, page 14 of 14). If the requalification studies do not include the proposed container/closure system and loading patterns, please provide a rationale for the validation approach.
 - f. Please comment on whether bioburden is assessed for blister packs [REDACTED] (b) (4).
[REDACTED] If so, please provide recent historical data.
19. With regard to the exteriors of the droptainer container/closure system post [REDACTED] (b) (4) the application indicates that sterility testing of exteriors will be included as a product release test and as a shelf life test [REDACTED] (b) (4).
[REDACTED], yet it appears that Sections 3.2.P.5, nor 3.2.P.8 do not include any such testing of exteriors. Please clarify the intention regarding sterility testing of droptainer exteriors for product release and stability and provide revised Sections 3.2.P.5 and 3.2.P.8 (as necessary).
20. The information regarding the media fill simulations to validate the [REDACTED] (b) (4) is acknowledged; however, please provide the line speed and maximum duration of fill to be used for the subject drug product on each filling line.

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

Sincerely,

Navdeep

Bhandari -S

Digitally signed by Navdeep Bhandari -S
DN: c=US, o=U.S. Government, ou=MHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001220182,
cn=Navdeep Bhandari -S
Date: 2015.10.26 17:00:57 -0400

Navdeep Bhandari, Pharm.D. USPHS
Regulatory Health Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research Branch



NDA 208135

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Alcon Research, Ltd.
Attention: Paul Nitschmann, MD
Head, Regulatory Affairs Pharma
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your New Drug Application (NDA) dated and received April 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for tetracaine hydrochloride ophthalmic solution, 0.5%. We also refer to your amendment dated May 28, 2015.

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 was 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 29, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 8, 2016.

We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues, which were communicated to you on June 29, 2015 (Clinical, PREA Requirement, Pediatric Assessment, and Regulatory), and July 1, 2015 (CMC):

I. CLINICAL

1. Your submission did not specify the search criteria used to select the submitted publications. Please provide your search criteria including the key words used in the literature search. If you have not done so, please perform a comprehensive search of all available literature including controlled studies that evaluated different concentrations, doses and dosing regimens. Include articles written in English as well as any articles written in a non-English language. For all non-English articles, please provide full English translations, as specified in 21 CFR 314.50.
2. Based on the initial review of the publications currently included in your NDA, we have observed that none of the studies evaluating the anesthetic efficacy of tetracaine ophthalmic solution, 0.5% demonstrated superiority of tetracaine ophthalmic solution, 0.5% over a concurrent control group. In the four active control studies ((b) (4) , Barequet 2000, (b) (4) and Tsoumani 2010) equivalence appears to be claimed based on the numerically similar reported pain scores. In the absence of a defined non-inferiority margin, we disagree that equivalence can be claimed. If you intend to rely on studies demonstrating non-inferiority, please provide a non-inferiority margin and a justification for that non-inferiority margin.
3. In your submission, you state that the evidence for the efficacy of tetracaine lies in the many years of use of tetracaine as a rapid onset and short acting anesthetic. Additionally, it appears that you plan to use the favorable efficacy results from the two publications which evaluated the anesthetic efficacy of tetracaine ophthalmic solution, 1% against saline (Watson 1991 & Anninger 2007) as supportive evidence. We acknowledge that tetracaine has many years of use and that data from different doses could potentially be used as supportive evidence. It is unclear why you have chosen the tetracaine ophthalmic solution, 0.5% as opposed to the tetracaine ophthalmic solution, 1%. Please provide an explanation for your choice, including why you did not choose to seek approval for the 1% concentration.

II. PREA REQUIREMENTS

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. Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you are required to submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting or in the absence of an End-of-Phase 2 meeting, at the time of the Agency's request. We have not received a iPSP for this product. We request that you submit the required iPSP.

The iPSP must contain an outline of the pediatric study or studies that you plan to conduct or have conducted (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. The PSP should be submitted in PDF and Word format.

For additional guidance on the content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

III. PEDIATRIC ASSESSMENT

Your submission did not include a Pediatric Assessment, as required under 21CFR 314.55. We request that you submit such an assessment.

IV. REGULATORY

Your submission did not include the required forms for patent information, per 21 CFR 314.53(c) and financial disclosure, per 21 CFR 54.4(a)(1) and (3). We request that you submit the required forms.

V. CHEMISTRY, MANUFACTURING, AND CONTROLS

1. With regard to method suitability testing for the sterility test; to be performed at release of the finished drug product, it is acknowledged that a supplemental report is provided for testing with *A. niger*. Please provide the initial method suitability testing report that includes the other compendial organisms.
2. The regulatory specification provided in 3.2.P.5.1 indicates that the sterility test is to be performed for commercial production lots at release only. 3.2.P.8.2 page 1 of 2 states that sterility testing will be performed at expiry and beyond for primary stability batches. For commercial lots placed in the stability program post-approval, please clarify if the sterility test is performed at release as well as at expiry and beyond as part of the stability program.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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.

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
07/10/2015



NDA 208135

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Paul Nitschmann, M.D., Head, Regulatory Affairs Pharma, Alcon Research, Ltd.
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 15, 2015, in order to continue our evaluation of your NDA.

1. With regard to method suitability testing for the sterility test; to be performed at release of the finished drug product, it is acknowledged that a supplemental report is provided for testing with *A. niger*. Please provide the initial method suitability testing report that includes the other compendial organisms.
2. The regulatory specification provided in 3.2.P.5.1 indicates that the sterility test is to be performed for commercial production lots at release only. 3.2.P.8.2 page 1 of 2 states that sterility testing will be performed at expiry and beyond for primary stability batches. For commercial lots placed in the stability program post-approval, please clarify if the sterility test is performed at release as well as at expiry and beyond as part of the stability program.

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

Sincerely,

Balajee
Shanmugam -S

Digitally signed by Balajee Shanmugam -S
DN: cn=U.S. Government, ou=HHS,
ou=FDA, ou=People,
o=S:2342.19200300.100.1.1=1300217143,
cn=Balajee Shanmugam -S
Date: 2015.07.01 14:43:07 -04'00'

Balajee Shanmugam, Ph.D.
Acting Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch



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

COMMUNICATION SHEET

DATE: June 29, 2015

To: Paul Nitschmann, MD Head, Regulatory Affairs Pharma	From: Eithu Lwin, PharmD Regulatory Project Manager
Company: Alcon Research, Ltd.	Division of Transplant and Ophthalmology Products
E-mail: paul.nitschmann@alcon.com	Email: Eithu.Lwin@fda.hhs.gov
Phone Number: 860-759-3584	Phone Number: 301-796-0728

Subject: Find enclosed comments for NDA 208135

Total no. of pages including cover: 4

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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 Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

NDA 208135

Tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT

Sponsor: Alcon Research, Ltd.

Attention: Paul Nitschmann, MD

Dear Dr. Nitschmann,

Upon initial review of your NDA 208135 submission for tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT submitted and received on April 30, 2015, we have the follow comments and requests for additional information.

CLINICAL

1. Your submission did not specify the search criteria used to select the submitted publications. This makes it difficult for us to determine whether you have conducted a comprehensive search. Please provide your search criteria including the key words used in the literature search to aid a cross-check and further search. If you haven't done so, please perform a comprehensive search of all available literature including controlled studies that evaluated different concentrations, doses and dosing regimens. Include articles written in English as well as articles written in a non-English language. For all non-English articles, please provide full English translations, as specified in 21 CFR 314.50.
2. Based on the initial review of the publications currently included in your NDA, we have observed that none of the studies that evaluated the anesthetic efficacy of 0.5% tetracaine ophthalmic solution showed statistically significant superiority of 0.5% tetracaine ophthalmic solution either against saline (Carden 1998 & Kim 2003) or against lidocaine 2% gel (b) (4), Barequet 2000, (b) (4) and Tsoumani 2010). The conclusion of similar effect with lidocaine 2% in the four active control studies ((b) (4), Barequet 2000, (b) (4) and Tsoumani 2010) seems to be made based on the numerically similar reported pain scores. From our perspective, to be able to make an equivalence claim, an appropriate equivalence margin needs to be specified.
3. In your submission, you state that the evidence for the efficacy of tetracaine lies in the many years of use of tetracaine as a rapid onset and short acting anesthetic. Additionally, it appears that you plan to use the favorable efficacy results from the two publications which evaluated the anesthetic efficacy of 1% tetracaine ophthalmic solution against saline (Watson 1991 & Anninger 2007) as supportive evidence. We acknowledge that tetracaine has many years of use and that data from different doses could potentially be used as supportive evidence. It is unclear why you have chosen the 0.5% tetracaine solution as opposed to the 1% tetracaine solution. Please provide an explanation for your choice, including why you did not choose to seek approval for the 1% concentration.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. You have not submitted your iPSP. We request that you submit the required iPSP no later than July 27, 2015.

The iPSP 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. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PEDIATRIC ASSESSMENT

Your submission did not include a Pediatric Assessment, as required under 21CFR 314.55. We request that you submit such assessment no later than July 27, 2015.

REGULATORY

Your submission did not include the required forms for patent information, per 21 CFR 314.53(c) and financial disclosure, per 21 CFR 54.4(a)(1) and (3). We request that you submit such forms no later than July 27, 2015.

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

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
06/29/2015
NDA 208135 IR 6/29/2015



NDA 208135

NDA ACKNOWLEDGMENT

Alcon Research, Ltd.
Attention: Paul Nitschmann, MD
Head, Regulatory Affairs Pharma
6201 South Freeway
Mail Stop: TC-45
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

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

Name of Drug Product: tetracaine hydrochloride ophthalmic solution, 0.5%

Date of Application: April 30, 2015

Date of Receipt: April 30, 2015

Our Reference Number: NDA 208135

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 June 30, 2015, 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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208135** submitted on April 30, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

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

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

If you have any questions, 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
05/14/2015
NDA 208135 Ack Letter



PIND 115866

TELECONFERENCE MINUTES

Alcon Research, Ltd.
Attention: Mr. Richard O. Reese
Global Project Regulatory Manager
External Disease and Exploratory Projects
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Reese:

Please refer to your Pre-Investigational New Drug Application (PIND) file for tetracaine hydrochloride, 0.5% STERI-UNIT.

We also refer to the teleconference scheduled between representatives of your firm and the FDA for April 17, 2013. The purpose of the teleconference was to gain concurrence on the requirements for the submission of an NDA for tetracaine hydrochloride ophthalmic solution 0.5% STERI-UNIT for {indication}.

Your April 16, 2013, e-mail to me stated that it would be acceptable to cancel this teleconference as the April 15, 2013, preliminary comments sent to you adequately addressed the questions submitted in the March 12, 2013, Meeting Package. The attached will serve as the minutes of this cancelled teleconference.

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

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Application Number: PIND 115866
Product Name: tetracaine hydrochloride, 0.5% STERI-UNIT
Indication: procedures in which a rapid and short acting topical ophthalmic anesthetic is indicated
Sponsor/Applicant Name: Alcon Research, Ltd.

BACKGROUND

A December 13, 2012, correspondence, received December 13, 2012, from Alcon Research, Ltd. (Alcon) requested a meeting for PIND 115866 to gain concurrence on the requirement for the submission of an NDA.

Indication noted for this product in the December 13, 2012, submission was for procedures in which a rapid and short acting topical ophthalmic anesthetic is indicated.

A Meeting Request Granted letter issued on January 3, 2013, stating April 17, 2013, as the agreed upon teleconference date. The March 12, 2013, Meeting Package was received on March 13, 2013. Meeting Preliminary Comments were sent, via e-mail, on April 15, 2013.

On April 16, 2013, Alcon Research, Ltd. sent via e-mail (Attachment 1), a request to cancel the meeting, stating that the preliminary comments sent April 15, 2013, adequately addressed the questions in the Meeting Package. On April 16, 2013, the Agency sent, via e-mail, a response that the cancellation of the teleconference was accepted.

DISCUSSION

Following, in **bold**, are the questions submitted in the March 12, 2013, Meeting Package. The FDA responses to these questions sent via e-mail on April 15, 2013 are in *italics*.

Quality:

1. **Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT® has been used for over 50 years without safety concerns and no other alternative for this drug exists at this time.** (b) (4)

Evaluations and efforts were conducted to reduce the levels of (b) (4) however, it is unclear if these modifications will be successful. Considering

that this single dosage product has been used for 50 years without safety concerns and meets the maximum daily exposure proposed limits, does the Agency agree that the drug product could be approved using the current manufacturing (b) (4) sterilization process which exposes the product to (b) (4)

FDA Response:

From a sterilization perspective, we agree that such a cycle might be capable of sterilizing the outside of the bottle (and the inside of the blister package). This is a review issue and the complete (b) (4) sterilization validation data should be submitted for review in the NDA.

To properly evaluate (b) (4) in the final drug product for preclinical and clinical safety, we need a description of the 50 year manufacturing history of your tetracaine product. This should include any major changes to the manufacturing process and the date when you first began utilizing the current (and any previous) (b) (4) sterilization process. The more specific the information you can provide regarding the history of the product and its (b) (4) related impurities, the better. This will allow us to make a determination of the acceptability of the supportive preclinical and clinical data from the literature.

2. In the event that the Agency does not agree with using the current manufacturing (b) (4) sterilization process, does the Agency agree that the drug product could be approved using a modified (b) (4) sterilization process which would expose the product to (b) (4) for a reduced amount of time?

FDA Response:

As in the response to Quality Question #1, the adequacy of any (b) (4) process, and its validation, is a review issue which will be assessed following submission of the NDA.

Nonclinical:

3. Alcon plans to provide a literature-based review of nonclinical safety and pharmacokinetics data [detailed information provided in briefing document]. Does the agency agree that the literature based review meets the requirements for the approval of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT®?

FDA Response:

If no issues of concern are raised upon review of the data, the Division concurs that a literature review is sufficient. The submission should include a summary of all published nonclinical literature being relied upon to support the NDA, and a copy of all the publications cited.

4. The analytical testing of marketed Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT® revealed two (b) (4) and two impurities. Relative to the active ingredient, the (b) (4) is approximately

(b) (4) is less than (b) (4)%, and (b) (4) is approximately (b) (4)% [please see the Quality section of the briefing document]. Based on the Company Position described below, does the Agency agree that no additional animal testing is required?

FDA Response:

See response to Nonclinical Question 1.

5. Should the impurity levels observed with the current manufacturing process be unacceptable, Alcon has also developed an alternative process that further reduces the levels of the (b) (4) and impurities [please see Quality section of the briefing document]. Compared to those previously measured, the (b) (4) has been reduced to less than (b) (4)% of the active ingredient, and the other impurities are either not detected or well below (b) (4)% of the active ingredient. Based on the discussion in the Company Position does the Agency agree that no additional animal testing is required?

FDA Response:

See response to Nonclinical Question 1.

Pharmacokinetic:

6. Alcon plans to submit an NDA for Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT®. No additional non-clinical pharmacokinetic/ADME studies are planned for this submission. Supportive documentation will be limited to available literature. All available and relevant non-clinical literature will be presented in the NDA. Does the FDA agree with this approach of a limited non-clinical section and not conducting any additional non-clinical ADME studies for this submission?

FDA Response:

The Agency agrees, provided adequate PK data/literature are available. Please note that, (b) (4)

7. Alcon plans to submit an NDA as per the proposed draft label for Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT®. No additional clinical PK or clinical pharmacology studies are planned for this submission. Supportive documentation will be limited to available literature. Available and relevant published clinical pharmacokinetics and clinical pharmacology literature for tetracaine will be presented in the NDA. Does the FDA agree with this approach of using published literature in the NDA and not conducting any additional clinical PK or clinical pharmacology studies for this submission?

FDA Response:

Yes, we agree.

Clinical:

- 8. Alcon plans to provide a literature-based review of clinical safety, pharmacokinetics and pharmacovigilance data. Does the agency agree that the literature-based review meets the requirements for the approval of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT®?**

FDA Response:

Approvability is a review issue, but a literature based NDA submission for clinical safety, pharmacokinetics and pharmacovigilance data would be acceptable.

- 9. Alcon has provided a synopsis and the associated statistical analysis plan for a proposed efficacy and safety study. In the event that a study is required, does the Agency agree that the study (b) (4) meets the requirements for approval of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT®, for the indication stated in the draft clinical label provided?**

FDA Response:

Approvability is a review issue, although we think it is likely that there is sufficient information in the clinical literature to support the efficacy of your product. We do not recommend that you utilize a contralateral eye study design; it is preferable to conduct randomization by patient or by eye to minimize patient bias. The protocol synopsis otherwise appears acceptable, but we will need to review the actual protocol and statistical analysis plan when available to provide additional comment.

The statistical analysis for the proposed study design is acceptable. However, we recommend you consider a less restrictive covariance matrix (instead of a compound symmetric covariance matrix) to model the residual correlation among repeated measurements. Also, we recommend two additional analyses: (1) construct a 95% confidence interval for the difference in response rates between the test product and the vehicle; (2) perform a McNemar's test for the primary endpoint.

- 10. Alcon believes the proposed analytical strategy as described in the draft statistical analysis plan adequately addresses the objectives of the proposed study. Does the Agency agree?**

FDA Response:

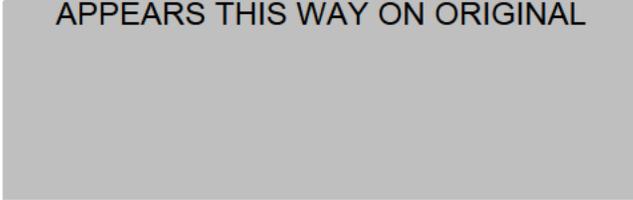
We will need to review the actual protocol and statistical analysis plan when available to provide additional comment. See Response to Question 9.

ATTACHMENTS

Attachment 1 April 16, 2013, e-mail from Alcon Research, Ltd. to include response from FDA

Attachment 1

APPEARS THIS WAY ON ORIGINAL



From: Almoza, Lois
Sent: Tuesday, April 16, 2013 11:26 AM
To: 'Reese, Richard'
Subject: RE: Preliminary Meeting Comments - PIND 115866\tetracaine hydrochloride 0.5% STERI-UNIT\Alcon Research, Ltd.

Good Morning Richard,

The Agency is fine with the cancelling of the meeting for tomorrow. We look forward to Alcon's official response to our meeting comments next week.

Regards,

Lois

From: Reese, Richard [<mailto:richard.reese@alcon.com>]
Sent: Tuesday, April 16, 2013 10:49 AM
To: Almoza, Lois
Subject: RE: Preliminary Meeting Comments - PIND 115866\tetracaine hydrochloride 0.5% STERI-UNIT\Alcon Research, Ltd.

Thank you Lois.

I just talked with the Therapeutic Unit and Project Heads. We agree with all comments received and feel that there is no longer a need to meet tomorrow.

With the Division's concurrence, Alcon would like to cancel the meeting.

I'll send in an official response to the comments electronically to the IND. Targeting early next week for submission.

Is the Agency in agreement with my proposals?

Best regards,

Richard

Richard Reese

Global Project Regulatory Manager

External Disease and Exploratory Projects

6201 South Freeway, M/C R3-54 | Fort Worth, TX 76134-2099, USA

T +1 817 551 4345 | F +1 817 551 4630 | Richard.Reese@alcon.com

Alcon

a Novartis company

From: Almoza, Lois [<mailto:Lois.Almoza@fda.hhs.gov>]

Sent: Monday, April 15, 2013 7:45 AM

To: Reese, Richard

Subject: Preliminary Meeting Comments - PIND 115866\tetracaine hydrochloride 0.5% STERI-UNIT\Alcon Research, Ltd.

Good Morning,

Please find preliminary comments to the 10 questions from your meeting briefing package attached.

Thank you,

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Reference ID: 3301462

Reference ID: 3899384

Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
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/

LOIS A ALMOZA
04/30/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹											
NDA # 208135 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: N/A Established/Proper Name: tetracaine hydrochloride Dosage Form: ophthalmic solution, 0.5%		Applicant: Alcon Research, Ltd. Agent for Applicant (if applicable):									
RPM: Eithu Z. Lwin		Division: Division of Transplant and Ophthalmology Products									
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 2/19/2016</p> <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>									
<p>• Actions</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 29, 2016</u> </td> <td style="width: 30%;"> <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR </td> </tr> <tr> <td> <ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> </td> <td> <input checked="" type="checkbox"/> None </td> </tr> <tr> <td> ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ </td> <td> <input type="checkbox"/> Received </td> </tr> <tr> <td colspan="2">❖ Application Characteristics³</td> <td></td> </tr> </table>			<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 29, 2016</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 	<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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received	❖ Application Characteristics ³		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 29, 2016</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR										
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 	<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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received										
❖ Application Characteristics ³											

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

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

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

Review priority: Standard Priority
 Chemical classification (new NDAs only): 7
 (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 via DARRTS
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ 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.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval 2/29/2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Received 4/30/2015
❖ 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
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Not requested
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 6/25/2015 DMEPA: <input type="checkbox"/> None 1/12/2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 1/27/2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None ADL 2/28/2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	7/14/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) Cleared date 2/26/2016 Archived in DARRTS 2/29/2016
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 2/29/2016
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>01/20/2016</u> If PeRC review not necessary, explain: _____ 	PeRC Meeting Minutes 2/4/2016
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • 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>) <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"> ❖ 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>) 	2/26/2016, 2/3/2016, 1/14/2016, 1/11/2016, 12/20/2015, 11/24/2015, 10/26/2015, 7/10/2015, 7/1/2015, 6/29/2015, 5/14/2015
<ul style="list-style-type: none"> ❖ 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) 	internal tcon memo 2/29/2016
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg PIND 115866, WRO Meeting minutes: 4/30/2013
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/29/2016
Deputy Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/26/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/29/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	01/20/2016 Filing Review 7/7/2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<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 checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 8 of Clinical Review 1/20/2016
• Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review cosigned primary review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/21/2016 Filing Review 6/30/2015

⁵ 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).

Clinical Pharmacology <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)	<input type="checkbox"/> None 10/13/2015 Filing Review 6/23/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Nonclinical <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)	<input type="checkbox"/> None 2/25/2016, 1/25/2016 Filing Review 6/8/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• 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)	<input type="checkbox"/> None 2/26/2016, 1/25/2016 Filing Review 6/30/2015
❖ 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)	See page 47 of Integrated Quality Assessment Addendum 2/26/2016
<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 (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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