

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208135Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 208135	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: n/a Established/Proper Name: tetracaine hydrochloride Dosage Form: ophthalmic solution Strengths: 0.5%		
Applicant: Alcon Research, Ltd.		
Date of Receipt: April 30, 2015		
PDUFA Goal Date: February 29, 2016		Action Goal Date (if different):
RPM: Eithu Z. Lwin, PharmD		
Proposed Indication(s): For procedures requiring a rapid and short-acting topical ophthalmic anesthetic		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Clinical and Nonclinical

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

**The Applicant has marketed the product without an approved application in the United States since 1959. This application relies solely on published scientific literature for safety and effectiveness. This published literature describes adequate and well controlled studies not conducted or sponsored by Alcon. The drug product is scientifically bridged to the published literature because at least two of the publications contained data generated from adequate and well controlled studies using the Alcon product, while other described studies do not name a listed drug and used the same active pharmaceutical ingredient in the same concentration as that contained in the proposed drug product. This information is scientifically relevant because it provides further evidence to support the efficacy and safety of the active ingredient because the drug product is a solution applied topically, which ensures that the drug product is delivered to the site of action, where the pharmacodynamic effect (anesthesia) of the product is achieved within 10-20 seconds after instillation.**

#### RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO

*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If "NO," proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If “NO” to (a) proceed to question #11.

If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A  YES  NO

If this application relies only on non product-specific published literature, answer “N/A”  
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A  YES  NO

If this application relies only on non product-specific published literature, answer “N/A”  
If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**Pharmaceutical alternative(s): There are several products that have been approved containing tetracaine in combination with other products (some of these NDAs/ANDAs have been withdrawn or discontinued, but others are currently marketed). The applicant relied on none of these applications to support approval of NDA 208135.**

**Approved June 29, 2006: NDA 21717/lidocaine and tetracaine 7%/ 7% cream for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.**

**Approved June 23, 2005: NDA 21623/lidocaine 70mg and tetracaine 70mg topical patch for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodesiccation and shave biopsy of skin lesions.**

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**Attachment:**  
**505(b)(2) Clearance**

**From:** Holovac, Mary Ann  
**Sent:** Friday, February 26, 2016 2:58 PM  
**To:** Lwin, Ei Thu  
**Cc:** Schumann, Katherine; Goldstein, Beth A (Duvall); Holovac, Mary Ann  
**Subject:** N208135 Tetracaine - cleared for action

Eithu,

We discussed this application at last Monday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

No additional changes are needed on the assessment provided to me on 2/26/16 assuming you are heading toward an approval action. If the application is not approved this cycle, you may defer archiving in darfts until you are heading toward approval in which case you would need clearance again from the committee-and you should let me know when the resubmit arrives.

Please let me know if you have any questions.

Mary Ann

**From:** Lwin, Ei Thu  
**Sent:** Friday, February 26, 2016 1:51 PM  
**To:** Holovac, Mary Ann  
**Subject:** NDA 208135 Tetracaine bridging

Hi Mary Ann,

Please see the attached revised 505b2 assessment.

Thank you,  
Eithu

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EI THU Z LWIN  
02/29/2016  
NDA 208135 505(b)(2) assessment and clearance

**Division of Transplant and Ophthalmology Products (DTOP)  
Acting Associate Director for Labeling (ADL) Review  
of the Prescribing Information**

<b>Product Title</b>	Tetracaine HCl Ophthalmic Solution 0.5% STERI-UNIT®
Applicant	Alcon Research, Ltd
Application/Supplement Number	NDA 208135/N-0000
Type of Application/Submission	505(b)(2) [ <i>literature based</i> ]
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	Y
Is Labeling Being Converted to PLLR? (Y/N)	Y
Proposed Indication(s) (if applicable)	For procedures requiring a rapid and short-acting topical ophthalmic anesthetic.
Approved Indication(s) (if applicable)	NA
Date FDA Received Application	April 30, 2015
Review Classification (Priority/Standard)	Standard
Action Goal Date	February 29, 2016
Review Date	February 26, 2016
Reviewer	Jin Chen, MD, PhD, ADL (acting)

**BACKGROUND**

The submission is a literature-based 505(b)(2) NDA for an unapproved marketed ophthalmic anesthetic, *Tetracaine HCl Ophthalmic Solution 0.5%*. The proposed indication is for procedures requiring a rapid and short-acting topical ophthalmic anesthetic through topical ophthalmic instillation. The same product has been marketed in the US as an unapproved drug for over 45 years by the same sponsor and other pharmaceutical companies (such as Bausch & Lomb) for a similar indication.

The proposed labeling submitted in the NDA appears simply converted from the current labeling of the unapproved marketed products. The labeling format was compliant with *Physician Labeling Rule* (PLR) and *Pregnancy and Lactation Labeling Rule* (PLLR) requirements. The labeling has been extensively reviewed by the NDA review teams with one negotiation with the sponsor when this reviewer started the detail as Acting ADL and to participate in the labeling review approximately 3 weeks prior to the PDUFA due date.

Outstanding concerns on the labeling contents were raised during these weeks of the review cycle with the following three sections (Table 1): *Contraindication (4)*, *Adverse Reactions (6.2)* and *Pregnancy (8.1)*. The Division did not believe that the sponsor had provided sufficient evidence to support their proposal.

This purpose of this review is primarily to focus on the sponsor’s proposed contraindication and (b) (4) in the Adverse Reactions section based on brief literature search and review. The recommendations on labeling revisions are reflected in the sponsor’s final version of the labeling dated February 25, 2016.

**Table 1. The major issues of the sponsor’s proposed labeling**

Sponsor’s Proposal	Division’s Revision
<b>4 CONTRAINDICATIONS</b>	<b>4 CONTRAINDICATIONS</b>
(b) (4)	
<b>6 ADVERSE REACTIONS</b>	<b>6 ADVERSE REACTIONS</b>
(b) (4)	
<b>8 USE IN SPECIFIC POPULATIONS</b>	<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>	<b>8.1 Pregnancy</b>
(b) (4)	[Yes, accepted]

## INFORMATION SOURCES

The following information has been used for the discussion on the labeling issues and to support recommendations on the labeling revisions:

**Literature reports** (limited search on (b) (4) to local anesthetics)

- Case reports and case analysis studies
- Review articles (including UpToDate)
- DESI (Drug Efficacy Study Implementation) determination for ophthalmic benoxinate and proparacaine)

**Original NDA submission:**

- Clinical review (conducted by Dr. Jennifer Harris)
- Clinical pharmacology review (conducted by Dr. Yongheng Zhang)
- Sponsor’s Integrated Summary of Safety (ISS) and two major cited review articles

**Current labeling of the following related products:**

- Tetracaine ophthalmic solution
- Proparacaine ophthalmic solution
- Benoxinate ophthalmic solution

**Data-Mining of FAERS database:**

- Ingredient(S): tetracaine
- MedDRA hierarchy level: preferred term (PT)

**CONTRAINDICATION (4) AND ADVERSE REACTIONS (6.2)**

The high-level literature review and datamining analysis of FAERS database did not suggest tetracaine after a topical ocular instillation was directly associated with (b) (4). There is insufficient evidence to support the addition of the term (b) (4) as a Contraindication and the (b) (4) proposed for inclusion under Adverse Reactions (b) (4) for *Tetracaine HCl Ophthalmic Solution 0.5%*.

**Original NDA submission:**

According to the clinical review and the sponsor's ISS, only one case of (b) (4) was listed as a non-SAE in a table under the Postmarketing Experience. Based on the MedWatch form that the sponsor provided, the (b) (4) was reported from a physician's office, and was believed not related to ophthalmic anesthetic in a follow-up report. No other (b) (4), either systemically or ocularly associated with this product, was reported in the NDA submission and in the two major review articles (McGee 2007<sup>1</sup> and Havener 1983<sup>2</sup>) that the sponsor primarily relied on for the ISS. The sponsor stated that the (b) (4) under Adverse Reactions was taken from the labeling of tetracaine ophthalmic solution marketed by other company ( (b) (4) ).

In response to the Division's requests for supporting evidence for the (b) (4), the sponsor replied "We did not find any such cases of (b) (4) in our database, nor did we find convincing cases in the literature."

By reviewing the labeling of currently marketed ophthalmic anesthetics, including tetracaine, proparacaine and benoxinate, we noted that all these products carry the similar text of the (b) (4) in their labeling. Surprisingly, the language for this (b) (4) was actually located in the Drug Efficacy Study Implementation (DESI) destination published in the 1969 Federal Register (FR) notice<sup>3</sup>. The following text under the Adverse Reactions section for proparacaine and benoxinate was quoted from the DESI report:

(b) (4)

<sup>1</sup> McGee HT: Toxicities of topical ophthalmic anesthetics. *Expert Opin Drug Saf* 6: 637-640, 2007

<sup>2</sup> Havener WH: Anesthesia (Chapter 5), Havener's Ocular Pharmacology 1983

(b) (4)

Furthermore, Dr. Wiley Chamber tracked down the supporting evidence for this (b) (4) (b) (4) which was conveyed in the Agency's summary of post-DESI efficacy supplement for (b) (4). The source data were a case report study published in (b) (4). In this case report, seven patients experienced (b) (4) following topical ocular instillation of proparacaine solution containing (b) (4). It has been well known in the literature that (b) (4) can cause adverse reactions from (b) (4) on all structures of the eye<sup>5</sup>. (b) (4) was actually removed from the proparacaine ophthalmic solution as indicated in the Agency's (b) (4). In the past many years (b) (4) has become much less used as a (b) (4) for most ophthalmic products.

Tetracaine ophthalmic solution 0.5% in this NDA is a preservative-free and is not expected to pose the same (b) (4) as those old formulations containing (b) (4). Thus, the proposed labeling should not carry (b) (4) as contraindication and the (b) (4) (b) (4) under Adverse Reactions. This conclusion is also further supported by the following literature review and datamining analysis.

### **Literature review:**

Through a quick literature search primarily focusing on (b) (4) to local anesthetics, we failed to identify any (b) (4) case associated with topical ocular application of a local anesthetic. For other exposure routes, such as dental, dermal or spinal, the reporting frequencies of (b) (4) to local anesthetics are very low, mostly reported from outside US and the reported events may be also potentially confounded by (b) (4) contained in local anesthetic preparations. Among all suspected local anesthetics (ester or amide-types) associated with the (b) (4), tetracaine was least reported through any exposure routes in the literature. We have identified only 3 tetracaine cases, which were all associated with non-ophthalmic exposure and the (b) (4) were not serious.

So far no evidence suggests that the (b) (4) observed from non-ophthalmic exposure can be extrapolated to the topical ocular instillation. Thus, the chance for tetracaine to induce a (b) (4) after topical corneal exposure (or systemically) is remote, given the decades of use of tetracaine in the US.

### ***Tetracaine-associated case:***

- Case #1 ( (b) (4) from US): A 58-year-old Caucasian male ophthalmologist developed (b) (4) due to exposed to proparacaine ( (b) (4) (b) (4)) and cross-reacted to tetracaine after switched from proparacaine ( (b) (4) (b) (4)). Accident exposure to proparacaine triggered immediate relapse with severe (b) (4).

(b) (4)

- Case #2 ( (b) (4), from US): A 60-year-old Asian woman experienced (b) (4) after instilling ophthalmic anesthetic drop before laser eye surgery. (b) (4) was positive to both proparacaine and tetracaine.
- Case #3 ( (b) (4), from Germany): A 37-year-old woman developed (b) (4) following topical tetracaine applied to nasal mucosa before nasal endoscopy.. A re-challenge with tetracaine a week later, the same reactions reoccurred. The (b) (4) was negative to tetracaine and lidocaine.

### FAERS Database search:

A brief data-mining analysis of FAERS database was performed to identify potential signal of (b) (4) associated topical ocular instillation of tetracaine. “Tetracaine” was run as a suspected drug [“*Ingredient (S)*” dataset configure] against all *Preferred Terms (PTs)* in the entire FAERS database.

Eight cases of (b) (4) associated with tetracaine were identified. However, routes of exposure to tetracaine in these 8 cases were either non-ophthalmic or unknown: spinal (n=3), unknown (n=2), dermal (n=1), dental (n=1) and nasal/throat (n=1). Upon a brief review of the case narratives, all were confounded by other medications (including other local anesthetics), underlying medical conditions or with insufficient information to limit establishing a potential causal relationship.

Certain ocular adverse events associated with tetracaine were observed from the FAERS database, such as corneal epithelium defects, corneal infiltrates, corneal disorder and ulcerative keratitis. These adverse reactions appear more likely related to non-specific corneal toxicities due to chronic ocular exposure or abuse of tetracaine and/or other local anesthetics. The profile of the adverse corneal events appears consistent with the Warnings and Precautions of the proposed labeling for this product and similar products.

### PREGNANCY/RISK SUMMARY (8.1)

The Sponsor did not propose, and disagreed with the division’s revision, to include the mandatory statement about the (b) (4)

Through informal consult, the Division of Pediatric and Maternal Health (DPMH) concurred that this topical ocular product administered as one or a few drops during ocular surgery or ocular tonometry did not warrant inclusion of the background risk statement. Thus, the DPMH decision took into consideration not just the proposed statement but its value in the context of use for a short-acting anesthetic applied topically to the cornea.

(b) (4)

As per 21CFR201.57(c)(9)(i)(B), if a drug is systemically absorbed, the Risk Summary must include information about the (b) (4) general population in order to establish a basis for comparison (PLLR Guidance 2014). The sponsor's justification for not conveying the (b) (4) in the labeling was *“While Alcon acknowledges that this statement is mandatory for drugs with systemic absorption, Alcon is unaware of data that demonstrate that a few drops of topical tetracaine lead to meaningful exposure.”*

(b) (4) As per the clinical pharmacology reviewer, Dr. Yongheng Zhang, pharmacokinetics (PK) study on topical tetracaine ophthalmic solution has not been studied either by the sponsor or in the literature. The PK information submitted in the NDA was mainly derived from dermatological formulations. However, Dr. Zhang believes that it is reasonable to expect a low systemic exposure to tetracaine at the proposed dosing regimen of this product.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JIN CHEN  
02/28/2016

RENATA ALBRECHT  
02/28/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** January 27, 2016

**To:** Eithu Lwin, Regulatory Project Manager  
Division of Transplant and Ophthalmology Products (DTOP)

**From:** Meena Ramachandra PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT<sup>®</sup>,  
topical ophthalmic  
**NDA 208135**

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As requested in DTOP's consult dated July 9, 2015, OPDP has reviewed the draft PI and proposed carton and container labeling for Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT<sup>®</sup>.

OPDP reviewed the proposed substantially complete version of the PI titled, "tetracaine-pi-word.doc" received via the DTOP SharePoint website on January 20, 2016. OPDP's comments are provided in the attached version of the substantially complete labeling.

OPDP has also reviewed the version of the proposed carton and container labeling titled "tetracaine-labels-word.doc" accessed on the DTOP SharePoint website on January 21, 2016. OPDP recommends increasing the prominence and readability of "OPHTHALMIC SOLUTION" to be consistent with the text "TETRACAINE HYDROCHLORIDE 0.5%" on the bottle sticker, carton sticker, and blister label. OPDP has no further comments on the proposed carton and container labeling.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/  
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MEENA RAMACHANDRA  
01/27/2016

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** January 8, 2016  
**Requesting Office or Division:** Division of Ophthalmology Products (DTOP)  
**Application Type and Number:** NDA 208135  
**Product Name and Strength:** Tetracaine Hydrochloride Ophthalmic solution, 0.5%

**Product Type:** Single Ingredient  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Alcon  
**Submission Date:** April 30, 2015  
**OSE RCM #:** 2015-1593  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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## 1 REASON FOR REVIEW

This review responds to a request from DTOP to evaluate the proposed carton labeling, bottle label and prescribing information for Tetracaine Ophthalmic solution, an unapproved drug seeking formal approval. The applicant is proposing an indication for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Alcon is seeking approval of Tetracaine Hydrochloride Ophthalmic Solution, which is used for ophthalmologic surgical procedures requiring a rapid and short-acting topical ophthalmic anesthetic. Tetracaine Hydrochloride Ophthalmic Solution has been marketed in the United States as an unapproved drug and is now formally seeking NDA approval. The proposed product will continue to provide an anesthetic option in the ophthalmological setting.

We reviewed the proposed label and labeling and identified the following areas of vulnerability to errors.

- Readability and prominence of important information on the carton labeling and container label

## 4 CONCLUSION & RECOMMENDATIONS

We reviewed the label and labeling and identified that the proposed bottle label and blister and carton labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product.

### 4.1 RECOMMENDATIONS FOR ALCON

We recommend the following be implemented prior to approval of this NDA:

#### A. CARTON LABELING

1. It is unclear why packaging information (b) (4) is the most prominent information on a carton labeling of a drug, Tetracaine Hydrochloride Ophthalmic Solution 0.5 %. Please delete all information related to (b) (4) and replace it with information for Tetracaine Hydrochloride Ophthalmic Solution 0.5% on each appropriate panel of the carton labeling.
2. It is unclear as to why carton labeling (b) (4) product information. Please consider printing information Tetracaine Hydrochloride Ophthalmic Solution 0.5% directly on each appropriate panel of the carton labeling.
3. Add equivalent statement for consistency with naming policy, such as: \*Tetracaine Hydrochloride Ophthalmic 0.5% equivalent to tetracaine 0.44%.

#### B. TETRACAINE CARTON STICKER

1. See A.3 and revise carton sticker accordingly.
2. Increase the font size of the dosage form as it is part of the entire established name of the product to ensure sufficient prominence and readability.
3. Add route of administration, such as "For Ophthalmic Use" to help ensure the correct use of this product.
4. Add the net quantity per vial and per carton to the label. Ensure information is located away from the strength of the product (i.e., away from 0.5%).
5. Add "Rx only" statement to the label. However, ensure it does not compete for prominence with established name or route of administration of the product.
6. Add the statement "Sterile. Single-Use Unit. Discard Unused Portion" to ensure correct use of the product.

#### C. BOTTLE LABEL

1. See A.3 and revise bottle label accordingly.
2. Increase the prominence of established name “Tetracaine Hydrochloride Ophthalmic Solution” by bolding it or increasing font size.
3. Increase the prominence of the strength if space permits.
4. Reduce the size of the manufacturer name to help increase prominence of important product information.
5. Add route of administration, such as “For Ophthalmic Use” to help ensure the correct use of this product, if space allows. You may achieve that by decreasing manufacturer prominent name “Alcon”.
6. Reduce size and debold the Rx only information to help increase prominence of other important product information.

#### **D. BLISTER LABEL**

1. See A.3 and revise blister label accordingly.
2. Add route of administration, such as “For Ophthalmic Use” to help ensure the correct use of this product.
3. Reduce the prominence of the manufacturer name “Alcon” by decreasing font size and debolding to help accommodate inclusion of route of administration and to help increase prominence of important product information.
4. Debold the Rx only statement and reduce the size to help increase prominence of important product information.
5. Revise the (b) (4) sentence to “Sterile Until Opened, Protect From Light” to help ensure the correct use of this product.
6. Add the statement “Single-Use Unit. Discard Unused Portion” to ensure correct use of the product.

## **APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tetracaine that Alcon submitted on April 30, 2015.

<b>Table 2. Relevant Product Information for Tetracaine</b>	
<b>Initial Approval Date</b>	N/A - <i>Note: Unapproved drug</i>
<b>Active Ingredient</b>	Tetracaine hydrochloride
<b>Indication</b>	Procedures requiring a rapid and short-acting topical ophthalmic anesthetic
<b>Route of Administration</b>	Topical ophthalmic
<b>Dosage Form</b>	Ophthalmic Solution
<b>Strength</b>	0.5%
<b>Dose and Frequency</b>	One drop topically in the eye(s) as needed.
<b>How Supplied</b>	4 mL filled in 4-mL natural medium- or low-density polyethylene plastic DROP-TAINER® dispensers and natural low-density polyethylene tips with white polypropylene caps in a carton of 12. Each sterilized DROP-TAINER® dispenser is packaged in a clear PVC and Tyvek blister. This product does not contain a preservative.
<b>Storage</b>	2–25°C (36–77°F) Protect from light.
<b>Container Closure</b>	This package system is comprised of a natural medium density polyethylene ( (b) (4) ) round bottle with a natural low density polyethylene (LDPE) dispensing plug and a white polypropylene (PP) closure enclosed in a polyvinylidene chloride (PVC) blister with heat sealed Tyvek backing. The bottle and plug components will be sterilized by (b) (4), and the closure will be (b) (4). The filled bottle with plug and closure are sealed into the blister (b) (4). Tamper evidence is provided by the heat sealed Tyvek backing on the blister.

## APPENDIX B. PREVIOUS DMEPA REVIEWS

**B.1 Methods**

On December 9, 2015, we searched the L:drive using the terms, tetracaine to identify reviews previously performed by DMEPA.

**B.2 Results**

Our search did not identify previous label and labeling reviews of tetracaine.

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On December 9, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Canada Safety, PA Patient Safety
Search Strategy and Terms	Match Exact Word or Phrase: Tetracaine

### D.2 Relevant Results

1. Institute for Safe Medication Practices. Safety briefs: A three-in-one package insert?. ISMP Med Saf Alert Acute Care. 2010;15(6):2-3.

## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 9, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>1</sup>

<b>Date Range</b>	December 9, 2015
<b>Product</b>	Tetracaine [product name]
<b>Event (MedDRA Terms)</b>	<b>DMEPA Official FBIS Search Terms Event List:</b> Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

### E.2 Results

Our search retrieved 11 cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

### E.3 List of FAERS Case Numbers

<sup>1</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

#### **E.4 Description of FAERS**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Tetracaine labels and labeling submitted by Alcon on April 30, 2015.

- Bottle label
- Carton labeling – Steri-Units
- Blister label
- Carton sticker
- Prescribing Information (not listed)

### **G.2 Label and Labeling Images**

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

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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MICHELLE K RUTLEDGE  
01/08/2016

YELENA L MASLOV  
01/12/2016

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 208135 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: N/A Established/Proper Name: tetracaine hydrochloride Dosage Form: ophthalmic solution Strengths: 0.5%		
Applicant: Alcon Research, Ltd. Agent for Applicant (if applicable):		
Date of Application: April 30, 2015 Date of Receipt: April 30, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: February 29, 2016	Action Goal Date (if different):	
Filing Date: June 29, 2015	Date of Filing Meeting: June 22, 2015	
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input checked="" type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li><li>• The product is a Qualified Infectious Disease Product (QIDP)</li><li>• A Tropical Disease Priority Review Voucher was submitted</li><li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li></ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): PIND 115866 Preliminary Comments for telecon sent on April 15, 2013

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If affected by AIP, has OC been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	IR sent 6/29/2015
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		IR sent 6/29/2015
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>2</sup>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	IR sent 6/29/2015.
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 7/9/15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No MedGuide, PPI, or IFU included; no consult needed
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 7/9/15
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> April 17, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PIND 115866 telecon
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** June 22, 2015

**BACKGROUND:** NDA 208135 tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT was submitted as 505(b)(2) by Alcon Research, Ltd on April 30, 2015. Tetracaine hydrochloride ophthalmic solution 0.5% has been marketed in the United States as an “unapproved drug” since 1959. A pre-NDA teleconference was scheduled for April 17, 2013, under PIND 115866 to discuss the requirements for submission of an NDA for tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT. The teleconference was later cancelled as the Preliminary Comments sent on April 15, 2013, adequately addressed the questions in the Meeting Package.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Eithu Lwin	Y
	CPMS/TL:	Judit Milstein	Y
Cross-Discipline Team Leader (CDTL)	William M. Boyd		N
Deputy Division Director	Wiley A. Chambers		Y
Division Director	Renata Albrecht		Y
Clinical	Reviewer:	Jennifer Harris	Y
	TL:	William Boyd	N
Clinical Pharmacology	Reviewer:	Yongheng Zhang	Y
	TL:	Philip Colangelo	N
Biostatistics	Reviewer:	Abel Eshete	Y
	TL:	Yan Wang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aaron Ruhland	N
	TL:	Lori Kotch	Y
Product Quality (CMC) Review Team:	ATL:	Anamitro Banerjee	N
	RBPM:	Navi Bhandari	N
• Drug Substance	Reviewer:	Gene Holbert	N
• Drug Product	Reviewer:	Milton Sloan	Y
• Process	Reviewer:	Vidya Pai	N
• Microbiology	Reviewer:	Lisa Shelton	N
• Facility	Reviewer:	Vidya Pai	N
• Biopharmaceutics	Reviewer:	Banu Zolnik	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Balajee Shanmugam		N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Other attendees	Daphne Lin (Deputy Director, Division of Biometrics IV)		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>The published literature may have used the proposed product</p>
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BA/BE studies or to justify reliance on information described in published literature):	
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <p>• Is the product an NME?</p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p><b><u>Environmental Assessment</u></b></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <p>• Establishment(s) ready for inspection?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input checked="" type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>IRs sent 6/29/2015 &amp; 7/1/2015, awaiting Sponsor's response</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Renata Albrecht, Division Director	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): October 1, 2015	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTION ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

Version: 6/15/2015

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EI THU Z LWIN  
07/14/2015  
NDA 208135 RPM Filing Review

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Application:** NDA 208135

**Application Type:** New NDA

**Name of Drug/Dosage Form:** tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT

**Applicant:** Alcon Research, Ltd.

**Receipt Date:** April 30, 2015

**Goal Date:** February 29, 2016

### **1. Regulatory History and Applicant's Main Proposals**

NDA 208135 tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT was submitted as 505(b)(2) by Alcon Research, Ltd on April 30, 2015. Tetracaine hydrochloride ophthalmic solution 0.5% has been marketed in the United States as an "unapproved drug" since 1959. A pre-NDA teleconference was scheduled for April 17, 2013, under PIND 115866 to discuss the requirements for submission of an NDA for tetracaine hydrochloride ophthalmic solution, 0.5% STERI-UNIT. The teleconference was later cancelled as the Preliminary Comments sent on April 15, 2013, adequately addressed the questions in the Meeting Package.

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

### **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter during labeling negotiation. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required

## Selected Requirements of Prescribing Information

• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:** *They name of the drug product should be consistent, will address this at the time of labeling negotiation.*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *Name of established pharmacologic class was not included - local anesthetics- will address at the time of labeling negotiation.*

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

*Comment:*

### Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:* *No verbatim statement included, will address during labeling negotiation*

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:* *It is not right justified, will address during labeling negotiation.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

**NO**

32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** It current has "8.2 Lactation", should be corrected as

(b) (4)

(b) (4)

**YES**

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

Comment:

(b) (4)

(b) (4)

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EI THU Z LWIN  
06/25/2015  
NDA 208135 RPM PLR Format Reivew

JUDIT R MILSTEIN  
06/25/2015