CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205388Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205388	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Omidria Established/Proper Name: phenylephrine HCL and ketorolac tromethamine Dosage Form: ophthalmic injection		
Applicant: Omeros Corporation		
Date of Receipt: July 30, 2013		
PDUFA Goal Date: May 30, 2014	Action Goal Date (if different):	
RPM: Jacquelyn Smith		
Proposed Indication(s): maintaining pupil size by preventing intraoperative miosis and for reducing postoperative pain.		

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	Labeling Sections: Drug Interactions; Nonclinical; Overdosage
phenylephrine hydrochloride ophthalmic solution NDA 203510 Acular (ketorolac tromethamine ophthalmic solution) 0.5% NDA 019700	Labeling Sections: Overdosage

*each source of information should be listed on separate rows

Note: Although the items listed in the table above are not "essential" to the approval of the application, they would be needed to populate an appropriately detailed label for the product.

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The listed drug products are both approved for topical ophthalmic use and there is extensive experience with the use of both phenylephrine and ketorolac as topical products in ophthalmology. To bridge the difference in dosage forms to be able to rely on the listed products and the literature, Omeros conducted three nonclinical pharmacology studies and one GLP safety and toxicology study. The nonclinical studies conducted by Omeros confirmed the pharmacology of the components of Omidria and assessed the potential toxicity of phenylephrine and ketorolac when administered intracamerally both separately and together as they are in Omidria.

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 ☒

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 as labeled 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)
phenylephrine hydrochloride ophthalmic solution	NDA 203510	Y
Acular (ketorolac tromethamine ophthalmic solution) 0.5%	NDA 019700	Y

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.

Applicant is not relying on NDA 19645.

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:
NDA 203510 phenylephrine hydrochloride ophthalmic solution

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").

This application provides for a change in dosage form, from topical ophthalmic to ocular irrigating solution and it is a new combination.

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 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):

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 ☐

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

/s/

JACQUELYN E SMITH
06/04/2014

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

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

Memorandum

Date: April 14, 2014

To: Jacquelyn Smith, M.A., Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Products (OPDP)

Subject: NDA 205388
OMIDRIA™ (phenylephrine and ketorolac) injection 1%/0.3%

As requested in your consult request dated September 18, 2013, OPDP has reviewed the proposed draft labeling for OMIDRIA™ (phenylephrine and ketorolac) injection 1%/0.3% (Omidria).

OPDP'S comments are based on the substantially complete version of the PI titled, "Proposed labeling- 205388.doc," which was received via email from DTOP on April 7, 2014. OPDP's comments are attached in the clean substantially complete version of the PI.

OPDP has also reviewed the proposed carton and container labeling located at: \\cdsesub1\evsprod\nda205388\0000\m1\us\draft-carton-container-labels.pdf (submitted to FDA by the sponsor on July 30, 2013).

We recommend revising both the carton and container labeling to include the percentages of phenylephrine and ketorolac as listed in the proposed PI.

If you have any questions, please contact Christine Corser at Christine.corser@fda.hhs.gov or (301) 796-2653.

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

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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.

/s/

CHRISTINE G CORSER
04/14/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 11, 2014

TO: Jacquelyn Smith, Regulatory Project Manager
Sonal Wadhwa, M.D., Medical Officer
William Boyd, M.D., Medical Team Leader
Division of Transplantation and Ophthalmic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 205388

APPLICANT: Omeros Corporation

DRUG: Phenylephrine HCl/ ketorolac tromethamine (OMS302)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: [redacted] (b) (4) prevention of intraoperative miosis, and reduction of [redacted] (b) (4) postoperative ocular pain

CONSULTATION REQUEST DATE:	September 13, 2013
CLINICAL INSPECTION SUMMARY DATE:	April 14, 2014
DIVISION ACTION GOAL DATE:	April 30, 2014
PDUFA DATE:	May 30, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of phenylephrine HCl/ ketorolac tromethamine for the (b) (4), prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain.

The following pivotal studies were inspected in support of the indication:

Protocol C09-001, entitled A Study of Phenylephrine HCl's and Ketorolac Tromethamine's Ability, Alone and in Combination, to Maintain Mydriasis and Relieve Pain and Inflammation in Subjects Undergoing Unilateral Cataract Extraction with Lens Replacement (CELR)", and

Protocol OMS302-ILR-003, entitled "A Phase 3 Randomized, Double-Masked, Placebo-Controlled Study of the Effect of OMS302 on Intraoperative Pupil Diameter and early Postoperative Pain in Subjects Undergoing Intraocular Lens Replacement with Phacoemulsification", and

Protocol OMS302-ILR-004, entitled A Phase 3 Randomized, Double-Masked, Placebo-Controlled Study of the Pharmacokinetics of OMS 302 on Intraoperative Pupil Diameter and Early postoperative pain in Subjects Undergoing Intraocular lens Replacement with Phacoemulsification".

The clinical site of Drs. Dunn, Lim, and Marsico were selected for inspection because they were amongst the highest enrolling for their respective protocols.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	C09-001/ 190/ 43	15 Jan-5 Feb 2014	VAI
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-003/ 190/ 64	15 Jan-5 Feb 2014	VAI
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-004/ 190/ 80	15 Jan-5 Feb 2014	VAI
John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-003 195/ 68	17 Jan-4 Feb 2014	VAI
John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-004/ 195/ 62	17 Jan-4 Feb 2014	VAI
Nicholas P. Marsico, M.D. East West Eye Institute 420 E. 3rd St., Suite 603 Los Angeles, CA 90013	C09-001/ 198/ 32	15-22 Nov 2013	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Steven H. Dunn, MD
   Houston Eye Associates
   915 Gessner, Suite 250
   Professional Building #3
   Houston, TX 77024

   a. What was inspected: At this site for Protocol C09-001, 49 subjects were enrolledand 43 subjects completed the study. For Protocol OMS302-ILR-003, 69 subjects were randomized to treatment and 64 subjects completed the study. For Protocol OMS302-ILR-004, 80 subjects were enrolled and 75 subjects completed the study. The records of approximately 20% of the subjects in each of the three protocols were audited: 13 subject records for Protocol 003, 11 subject records for Protocol 001, and 14 subject records for Protocol 004. Records reviewed included, but were not limited to, informed consent forms, inclusion/exclusion criteria, randomization, source documents, case report forms (CRFs), hospital records, follow-up visits, IRB and sponsor correspondence, monitoring logs, and drug accountability.

   b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection with the following observations:

   <u>For Study C09-001:</u>

   1. Delayed evaluations of adverse events by the clinical investigator. For example:

      a. Subject 20145 had an adverse event "Fibrous Pupillary membrane formations" that was not evaluated by the investigator until the end of the study.

      b. Subject 10008 reported inflammation in October 2010 that was not evaluated until February 2011.

      c. Subject 20014 reported eye inflammation on October 14, 2010, that was not evaluated until January 2011.

      d. Subject 20015 reported eye pain/inflammation in October 2010 that was not evaluated until January 2011.

   2. Subjects 10009, 190045, 190025, and 200020 had visual acuity checks and intra-ocular pressure determinations performed by a study coordinator not delegated this responsibility. According to Dr. Dunn's written response, the study coordinator was an Ophthalmic Assistant certified to perform these procedures; however, the delegation log did not clearly document the delegation of these duties to the study coordinator.

   3. Approximately 20 subjects, including Subjects 2003, 20004, 20012, 10005, 20011, 20032, and 20033, did not have complete or accurate video recording of the ILR surgery as required in the study protocol for comparison and evaluation by the Sponsor.

For Protocol OMS302-ILR-003:

Subjects 190012, and 190069 had Day 7 Lens Status/ Iris Pupil Examinations performed by a study coordinator not delegated this responsibility.

For Protocol OMS302-ILR-004:

Subjects 190041 and 190044 had Day 14 and Day 90 Lens Status/Iris Pupil Examination performed by a study coordinator not delegated this responsibility.

For Protocols OMS302-ILR-003, and C-09-001:

Investigational drug disposition records were not adequate with respect to quantity and use by subjects. For example; Subjects in Study C09-001 Group 4 should have received 3.1 ml OMS-PE and 4.4 ml OMS-KE; Group 2 should have received 3.1 ml of OMS-PE. Subjects in Study ILR-003 should have received 4.4 ml. Quantities of drugs dispensed were not documented for any of the subjects in either study.

Dr. Dunn responded in writing in a letter dated February 19, 2014, to the observations on the FDA Form 483. Dr. Dunn provided copies of source documentation to support his explanation that the adverse events experienced by Subjects 20145, 10008, 20014, and 20015 were evaluated in a timely fashion as evidenced by the signature and date of either himself or his sub-investigator. The date on the source document some months after the occurrence of the adverse event was not an indication of the date of the investigator's evaluation of the adverse event but the investigator's acknowledgement of review of the accumulated adverse event data.

Dr. Dunn stated that intra-ocular pressure (IOP) and visual acuity (VA) assessments were performed by Ophthalmic Assistants (OAs) who were certified to perform such assessments. Dr. Dunn provided copies of source documentation indicating that these assessments were performed by the OAs.

Dr. Dunn noted that the video recordings did not necessarily contain a clear image of the randomization numbers; however, each video could be linked to the appropriate subject via identifiers in the video including subject initials and date of surgery.

Dr. Dunn noted that iris color assessments were performed by study coordinators while lens assessments were performed either by himself or the sub-investigator. Dr. Dunn acknowledged that multiple signatures/initials on the source documents made it unclear which individuals were responsible for conducting specific assessments. Dr. Dunn committed to ensuring that the Delegation of Authority Log would clearly indicate the tasks delegated to specific individuals and that signatures on future study documents would clearly indicate what tasks were performed and by whom they were performed.

Dr. Dunn acknowledged that the volume of study drug dispensed to prepare a subject's test irrigation solution for Protocols C09-001 and OMS302-IL-003 was not documented. In Dr. Dunn's written response, he provided an example of the "OMS302 Receipt and Dispensing Log". This log indicated the receipt dates and the dispensation dates of the test article, subject identifiers, and time of preparation of the test article. The Log did not contain a column to document the amount of test article withdrawn and added to the balanced salt solution (BSS). Lack of this documentation was noted in a sponsor audit. Corrective action included a Note to File to explain past practice and future procedures. The Note indicated that the correct amount of test article was withdrawn and used for all subjects, that the amount of test article added to the BSS solution was recorded on the subject randomization IVRS worksheet for the remaining subjects, and that going forward, the Dispensing Log would be revised so that the amount of test article withdrawn from the vial (e.g., 4.4 mL) for each instance of test article preparation would be documented. Dr. Dunn committed to capturing the amount of test article dispensed as part of the Dispensing Log or other source documents relevant to each subject.

c. Assessment of data integrity: There appears to be sufficient documentation to assure that the drug was available to the site, that the protocol contained specific instructions for preparation of the test article, that study kits were documented as received and used, and that subjects were dispensed the test article. OSI considers the available documentation, in conjunction with the investigators' written responses, to provide reasonable assurance that subjects were treated in compliance with the protocol; however, the review division may wish to consider whether the lack of documentation regarding the amount of test article withdrawn from the dispensing vials would adversely affect its assessment of safety and/or efficacy.

2. Nicholas P. Marsico, M.D.
   East West Eye Institute
   420 E. 3rd St., Suite 603
   Los Angeles, CA 90013

a. What was inspected: At this site for Protocol C09-001, 32 subjects were randomized and 30 subjects completed the study. The records of 23 subjects in Protocol C09-011 were audited. Records reviewed included, but were not limited to, informed consent forms, inclusion/exclusion criteria, financial disclosure forms, monitoring and IRB correspondence, protocol deviation forms, source documents and case report forms (CRFs). For six subjects, source documents were compared with the corresponding case report forms on compact disk as provided to the clinical site by the sponsor.

b. General observations/commentary: The primary efficacy endpoint of pupil diameter could not be audited as, per protocol, videotapes of the involved surgery were sent for interpretation to a blinded reader. This data was then forwarded to the sponsor. OSI informed the reviewing medical officer that the primary endpoint data was not available for review on site. The medical officer responded that the absence of this data on site was consistent with the design of the protocol, and that the review division would be reviewing selected tapes to check the reproducibility of the primary efficacy data.

A Form FDA 483 was issued at the conclusion of the inspection with a single observation noting that a corticosteroid (mistakenly referred to on the protocol deviation form as Vigamox) was dispensed post-operatively to all subjects without regard to their Summed Ocular Inflammation Score (SOIS), despite the protocol's requirement that the recipients of the corticosteroid exhibit an SOIS inflammatory score of 3 or greater.

c. Assessment of data integrity: The review division may wish to consider whether the post-operative dispensation of a corticosteroid to all subjects regardless of SOIS score would affect safety or efficacy considerations Other than this observation, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. John M. Lim, MD
Houston Eye Associates
915 Gessner, Suite 250
Professional Building #3
Houston, TX 77024

a. What was inspected: At this site for Protocol OMS302-ILR-003, 68 subjects were randomized to treatment and 67 subjects completed the study. For Protocol OMS302-ILR-004, 62 subjects were enrolled and 60 subjects completed the study. The records of 14 subjects for Protocol 003 and 13 subjects for Protocol 004 were audited. Informed consent forms were signed by all subjects for both studies prior to any treatment. Other records reviewed included, but were not limited to, inclusion/exclusion criteria, randomization, case report forms (CRFs), monitoring logs, IRB and sponsor correspondence, and drug accountability. Data in source documents were compared with FDA line listings and no discrepancies were noted.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection with the following observations:

<u>For Protocol OMS302-ILR-003:</u>

1. The investigation was not conducted in accordance with the investigational plan. For example:

   a. Subjects 001, 003, 009, 013, 055, and 062, had portions of visual examinations performed by study coordinators not delegated this responsibility. Also, Subject 062 experienced increased intra-ocular pressure as determined by a study coordinator, and this adverse event was not evaluated for approximately one month.

   b. Subjects 001, 002, 005, 013, 014, 026, 039, 049, and 058 did not have complete or accurate video recordings of the intra-ocular lens replacement (ILR) surgery as required by protocol.

2. Investigational drug disposition records were not adequate with respect to quantity and use by subjects. For example:

a. The quantity of drug dispensed to each subject was not documented.

b. Subjects 013, 020, and 027 received the study drug during ocular surgery; however, the kit number of the dispensed study drug was not documented.

For Protocol OMS302-ILR-004:

The investigation was not conducted in accordance with the investigational plan in that Subject 033 experienced an adverse event of ocular tearing and soreness on July 20, 2012; however, this adverse event was not evaluated by the investigator until three months later.

Dr. Lim responded to the above observations in a letter dated February 20, 2014. Dr. Lim emphasized that all subjects were seen and treated either by him or his sub-investigator and that other components of the ophthalmological exams were appropriately conducted by accredited Ophthalmic Assistants (OAs). Dr. Lim acknowledged that the Delegation Log was unclear in describing the assignment of responsibilities for specific components of the ophthalmic examinations. Dr. Lim committed to using better designed Delegation Logs that would clearly delineate specific study responsibilities.

Dr. Lim also stated that all adverse events were evaluated on the day of their occurrence. The date on the source document some months after the occurrence of the adverse event was not an indication of the date of the investigator's evaluation of the adverse event but the investigator's acknowledgement of review of the accumulated adverse event data. Dr. Lim committed to a re-design of the Adverse and Intercurrent Medical Events worksheet so that the specific dates for review of adverse events and the dates of review of accumulated/transcribed medical data would be clearly noted.

Dr. Lim acknowledged that the surgeries for several subjects were not recorded on video as required by protocol. Dr. Lim explained that incompatible DVD formats or other technical glitches prevented video recording. Dr. Lim noted that the lack of these recordings was reported as a protocol deviation.

Dr. Lim acknowledged that for Protocol OMS302-IL-003 that neither the kit numbers used at the time of surgery nor the volumes of study drug withdrawn and added to bottles of BSS at the time of test irrigation solution preparation were documented. Similar to the situation with Dr. Dunn (both investigators are part of the Houston Eye Associates), an audit revealed that the amount of test article withdrawn and added to the BSS was not documented. Again, the "OMS302 Receipt and Dispensing Log" lacked a column for capturing this information. As corrective action, a Note to File was generated indicating that the correct amount of test article was withdrawn and used for all subjects, that the amount of test article added to the BSS solution was recorded on the subject randomization IVRS worksheet for the remaining subjects, and that a revision was made to the Dispensing Log so that the amount of test article withdrawn from the vial (e.g., 4.4 mL) for each instance of test article preparation would be documented. During the study, the site also began to document the kit number of study drug used on the patient worksheet on the day of surgery.

c. **Assessment of data integrity:** There appears to be sufficient documentation to assure that the drug was available to the site, that the protocol contained specific instructions for preparation of the test article, that study kits were documented as received and used, and that subjects were dispensed the test article. OSI considers the available documentation, in conjunction with the investigators' written responses, to provide reasonable assurance that subjects were treated in compliance with the protocol; however, the review division may wish to consider whether the lack of documentation regarding the amount of test article withdrawn from the dispensing vials would adversely affect its assessment of safety and/or efficacy.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Marsico conducted Protocol C09-001, Dr. Dunn conducted Protocols C09-001, OMS302-ILR-003 and OMS302-ILR-004, and Dr. Lim conducted Protocols OMS302-ILR-003 and OMS302-ILR-004. Their conduct of their respective protocols was inspected in support of this NDA.

Dr. Marsico was issued a Form FDA 483. The final classification of this inspection was Voluntary Action Indicated (VAI). Other than the consideration noted above; i.e., dispensation of a corticosteroid to all subjects, the data generated by this clinical site and submitted by the sponsor appear adequate in support of the respective indication.

Drs. Dunn and Lim were issued Form FDA 483s. The final classification of these inspections was Voluntary Action Indicated (VAI). The amount of test article withdrawn from the dispensing vials was not documented for C09-001 and/or OMS302-IL-003. This lack of documentation was acknowledged by both Drs. Dunn and Lim. Both investigators implemented corrective actions to capture this data for subsequent study activities. There appears to be sufficient documentation to assure that the drug was available to the site, that the protocol contained specific instructions for preparation of the test article, that study kits were documented as received and used, and that subjects were dispensed the test article. OSI considers the available documentation, in conjunction with the investigators' written responses, to provide reasonable assurance that subjects were treated in compliance with the protocol; however, the review division may wish to consider whether the lack of documentation regarding the amount of test article withdrawn from the dispensing vials would adversely affect its assessment of safety and/or efficacy.

{See appended electronic signature page}

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Division of Good Clinical Practice Compliance
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/s/

ROY A BLAY
04/12/2014

JANICE K POHLMAN
04/14/2014

KASSA AYALEW
04/14/2014

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*****

Date of This Review:	April 4, 2014
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 205388
Product Name and Strength:	Omidria (Phenylephrine and Ketorolac) Injection, 1% / 3%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Omeros
Submission Date:	July 30, 2013
OSE RCM #:	2013-2174
DMEPA Primary Reviewer:	Rachna Kapoor, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and package insert for Omidria (Phenylephrine and Ketorolac) Injection, NDA 205388, for areas of vulnerability that could lead to medication errors.

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.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA identified trailing zero, a dangerous dose designation per Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] on the container label, carton labeling, and the dosage and administration section of the package insert. We provide recommendations to change the dangerous dose designation.

Additionally, DMEPA identified that the dosage form and the strength of the product was incorporated into the established name. The dosage form and strength should follow the established name. We provide recommendations to the Applicant to separate the dosage form and strength from the established name per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.[2]

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[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 Feb 20]. Available from: http://www.ismp.org/Tools/errorproneabbreviations.pdf

[2] 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Furthermore, DMEPA identified that the proprietary and established names are not prominent enough on the container label and carton labeling, which may introduce selection errors. As a result, we provided recommendations to increase the font size of the proprietary and established names to make this information more prominent.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton labeling, and package insert can be improved from a safety perspective by deleting some dangerous dose designations from the labeling and the dosage and administration section of the package insert. Additionally, the container label and carton labeling can be improved to ensure safe use of the product.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

4.1 COMMENTS TO THE DIVISION

4.1.1 Dosage and Administration Section of the Package Insert

i. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[3] appear in this section of the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

a. Remove the trailing zero after the decimal point in '4.0 mL' and replace with '4 mL' in this section of the package insert because the whole number can be mistaken as 40 mL if the decimal point is not seen.

4.2 COMMENTS TO THE APPLICANT

4.2.1 Container Label

i. Increase the font size of the established name to make it at least half the size of the proprietary name per 21 CFR 201.10(g)(2).

[3] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 Feb 20]. Available from: http://www.ismp.org/Tools/errorproneabbreviations.pdf

ii. Increase the font size of the proprietary name and the established name as these names should be the most prominent information on the label.

iii. Replace the statement [redacted] (b) (4) with '(Phenylephrine and Ketorolac) Injection 1% / 0.3%'. Per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors[4], the established name should be stated separate from the dosage form and the strength. For example,

Omidria

(Phenylephrine and Ketorolac) Injection

1% / 0.3%

iv. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[5] appear on container label. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

a. Remove the trailing zero after the decimal point in '4.0 mL' and replace with '4 mL' because the whole number can be mistaken as 40 mL if the decimal point is not seen.

4.2.2 Carton Labeling

i. See 4.2.1.i, 4.2.1.iii, 4.2.1.iv, and revise carton labeling accordingly.

[4] 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

[5] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 Feb 20]. Available from: http://www.ismp.org/Tools/errorproneabbreviations.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Omidria that Omeros submitted on September 27, 2013.

Table 2. Relevant Product Information for Omidria	
Active Ingredient	Phenylephrine hydrochloride and ketorolac tromethamine
Indication	[redacted] (b) (4) prevention of intraoperative miosis and reduction of early postoperative pain in intraoperative lens replacement surgery
Route of Administration	Ophthalmic irrigation
Dosage Form	Injection
Strength	1% / 0.3%
Dose and Frequency	4 mL diluted in 500 mL irrigation solution titrated to effect
How Supplied	Glass vials, each enclosed in a carton, 10 vials per cardboard box
Storage	Room temperature, protect from light

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L:Drive Med Err Consults Completed on March 14, 2014 using the terms, 'phenylephrine and ketorolac' to identify reviews previously performed by DMEPA.

B.2 Results

The proposed proprietary name Omidria was found acceptable from both a promotional and safety perspective in OSE RCM#2013-1321 and #2013-2257 for IND 78227 and NDA 205388 on November 7, 2013.

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/s/

RACHNA KAPOOR
04/04/2014

YELENA L MASLOV
04/07/2014

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 # 205388 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Omidria (phenylephrine-ketorolac) Established/Proper Name: Dosage Form: ophthalmic injection Strengths: 1% / (b) (4)		
Applicant: Omeros Agent for Applicant (if applicable): N/A		
Date of Application: July 30, 2013 Date of Receipt: July 30, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: May 30, 2013	Action Goal Date (if different):	
Filing Date: September 28, 2013	Date of Filing Meeting: September 17, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 4		
Proposed indication(s)/Proposed change(s): see orig. submission		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): asdfffsf

List referenced IND Number(s): 78227

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	S
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☐	☒		

User Fee Status ***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.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
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)].**	☐	☒	☐	
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)]?** ***If you answered yes to any of the above 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***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
		qwerqwerqwrewqr	

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
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), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	☒	☐		PeRC meeting is 10/30/13

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☒	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 12/7/11 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 2/28/13 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 17, 2013

BLA/NDA/Supp #: 205388

PROPRIETARY NAME: Omidria

ESTABLISHED/PROPER NAME: phenylephrine HCL-ketorolac tromethamine

DOSAGE FORM/STRENGTH: 1% / (b) (4)

APPLICANT: Omeros, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: Omeros, Inc submitted this NDA on July 30, 2013, and it was received electronically on July 30, 2013. Priority level is standard review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J. Smith	Y
	CPMS/TL:	D.Willard	
Cross-Discipline Team Leader (CDTL)	W. Boyd		Y
Clinical	Reviewer:	S.Wadhwa	Y
	TL:	W.Boyd	
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Y. Harigaya	Y
	TL:	P. Colangelo	Y
Biostatistics	Reviewer:	Y. Deng	Y
	TL:	Y. Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	M. Rivera	Y
	TL:	L. Kotch	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	M. Seggel	Y
	TL:	B. Shanmugam	Y
Quality Microbiology *(for sterile products)*	Reviewer:	S. Donald	Y
	TL:	B. Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority:

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JACQUELYN E SMITH
10/07/2013

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 205388

Application Type: New NDA

Name of Drug: Omidria (phenylephrine-ketorolac ophthalmic injection) 1% / (b) (4)

Applicant: Omeros

Submission Date: July 30, 2013

Receipt Date: July 30, 2013

1.0 Regulatory History and Applicant's Main Proposals

The applicant has submitted a New Drug Application (NDA) for Omidria (phenylephrine HCL/ketorolac tromethamine) for the (b) (4) prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the 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).

3.0 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. 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.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required

• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

***** RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement should be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The statement should be bolded.*

Product Title

NO 10. Product title in HL must be **bolded.**

Comment: *The product title should be bolded.*

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered 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**").

Comment:

Selected Requirements of Prescribing Information (SRPI)

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.****"*)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. 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

NO 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. 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

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Revision Date should be bolded.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment: *A horizontal line should be added.*

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. 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:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
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 (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. 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 patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. 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

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. 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**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

N/A 46. When clinical trials adverse reactions data is 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 clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is 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:

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

JACQUELYN E SMITH
10/02/2013