

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201923Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: August 28, 2014
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 201923
Product Name and Strength: Iluvien (Fluocinolone acetonide) Intravitreal Implant, 0.19 mg
Submission Date: August 27, 2014
Applicant/Sponsor Name: Alimera Sciences
OSE RCM #: 2014-1355-1
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Associate Director: Lubna Merchant, PharmD, MS

1 PURPOSE OF MEMO

The Division of Transplant and Ophthalmology Products requested that we review the revised tray labeling and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised tray labeling and carton labeling are acceptable from a medication error perspective.

¹ Kapoor, R and Maslov, Y. Label and Labeling Review for ILUVIEN (NDA 201923). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 AUG 05. 8 p. OSE RCM No.: 2014-1355.

APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 27, 2014

Tray Labeling



Carton Labeling



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/s/

RACHNA KAPOOR
08/28/2014

LUBNA A MERCHANT
08/28/2014

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

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

Memorandum

Date: August 13, 2014

To: Diana Willard, CPMS
Division of Transplant and Ophthalmology Products (DTOP)

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

Subject: NDA #201923
ILUVIEN[®] (fluocinolone acetonide intravitreal implant)

As requested in your consult request dated July 16, 2014, OPDP has reviewed the proposed draft labeling for ILUVIEN[®] (fluocinolone acetonide intravitreal implant).

OPDP'S comments are based on the substantially complete version of the PI titled, "Labeling from 3.26.14 Resubmission.doc," which was received via the DTOP Sharepoint website on August 11, 2014. OPDP's comments are attached in the clean substantially complete version of the PI.

OPDP notes that several areas of the label include notes to the drug sponsor requesting inclusion of additional data/information. OPDP was unable to provide comments on these areas of the label.

OPDP has also reviewed the proposed carton and container labeling located within the CDER/OSE/OMEPRM/DMEPA Labeling Review submitted into DARRTS on August 5, 2014. OPDP has no further comments on the proposed carton and container labeling.

Thank you for the opportunity to review this proposed labeling.

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

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

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/s/

CHRISTINE G CORSER
08/13/2014

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:	August 5, 2014
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 201923
Product Name and Strength:	Iluvien (Fluocinolone acetonide) Intravitreal Implant, 0.19 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Alimera Sciences
Submission Date:	July 16, 2014
OSE RCM #:	2014-1355
DMEPA Primary Reviewer:	Rachna Kapoor, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed tray labeling, carton labeling, and package insert for Iluvien (Fluocinolone acetonide) Intravitreal Implant, NDA 201923, 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
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA identified that the proprietary name, established name, dosage form, and strength need to be more prominent and legible for ease of identification for safe use of this product. We provide recommendations to the Applicant to increase the prominence of this information as per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.¹

¹ 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>

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed tray labeling and carton labeling can be improved to increase the prominence and readability of important information on the label to promote the safe use of the product.

Additionally, DMEPA concludes that the package insert is acceptable. We have no additional comments for the package insert at this time.

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

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. Tray Labeling

i.  (b) (4)

 We recommend this to promote readability and easy identification of the product as recommended in the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.²

ii. Consider increasing the font thickness for the established name, dosage form, and strength to make it more prominent on the label. This is required information that should be easily visible for safe identification and use of the product. This is consistent with the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.²

iii. Consider printing the proprietary name using Title case letter, followed by lower case letters in accordance with the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.² Otherwise, ensure all the letters in the proprietary name are the same font size to help increase readability of the proprietary name.

iv. Consider minimizing the logo above the proprietary name to increase the legibility of the name. This recommendation is consistent with the Draft

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>

Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.³

- v. Bold the statement [REDACTED] (b) (4) to highlight the correct route of administration. We recommend this revision to help prevent wrong route of administration errors.

B. Carton Labeling

- i. See A.i through A.v and revise carton labeling accordingly.
- ii. Ensure that all the panels on the carton labeling contain the proprietary name, established name, dosage form, and strength for ease of identification of the product.
- iii. Ensure the route of administration statement [REDACTED] (b) (4) appears on both the top panel and the principal display panel of the carton labeling. Additionally, ensure the sufficient prominence of this statement by increasing font size, bolding or some other means.
- iv. Consider increasing the intensity of color font of the information (e.g., established name, dosage form, strength, route of administration statement, etc.) written on the top and principal display panels. We recommend this revision to ensure sufficient readability of information.
- v. Add the statement of ingredients to the side panel of the carton labeling stating what is present in the unit dose intravitreal insert. For example, “Each intravitreal insert contains: fluocinolone acetonide 0.19 mg. Inactive ingredients: etc.” This recommendation is per the 21 Code of Federal Regulations 201.10.
- vi. Relocate the National Drug Code (NDC) number to the top panel and the principal display panel. As per the 21 Code of Federal Regulations 207.35 (b)(3), the NDC number should appear prominently in the top third of the principal display panel.

³ 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>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Iluvien that Alimera Sciences submitted on July 16, 2014.

Table 2. Relevant Product Information for Iluvien	
Active Ingredient	Fluocinolone acetonide
Indication	The treatment of (b) (4) diabetic macular edema
Route of Administration	Intravitreal
Dosage Form	Intravitreal insert
Strength	0.19 mg
Dose and Frequency	Insert into the posterior segment of the affected eye through a pars plana insertion. It is designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day. (b) (4)
How Supplied	A sterile single use preloaded inserter with a 25-gauge needle, packaged in a tray sealed with a (b) (4) lid
Storage	Store at 15° – 30°C (59° – 86°F)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on August 1, 2014 using the terms, fluocinolone to identify reviews previously performed by DMEPA.

C.2 Results

Two proprietary name reviews were completed for Iluvien under the application NDA 201923. The first review was completed on October 13, 2010 (OSE RCM#2010-1548) and the second review was completed on July 31, 2014 (OSE RCM#2014-25858). Both reviews found the name acceptable.

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,⁴ along with postmarket medication error data, we reviewed the following Iluvien labels and labeling submitted by Alimera Sciences on July 16, 2014.

- Inserter
- Tray Labeling
- Carton Labeling
- Package Insert (no image included)

G.2 Label and Labeling Images

Inserter



Tray Labeling



⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)



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/s/

RACHNA KAPOOR
08/05/2014

YELENA L MASLOV
08/05/2014

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: November 30, 2010

TO: Raphael Rodriguez, Regulatory Project Manager
Jane Dean, Regulatory Project Manager
Boyd, William M., M.D, Medical Team Leader
Martin P. Nevitt, M.D, Clinical Reviewer
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

RE: NDA 201923

SPONSOR: Alimera Sciences, Inc.
Contact: Barbara H. Bauschka, Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005
Phone #: 678 527 1330

DRUG: Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg

NEW MOLECULAR ENTITY (NME): No

REVIEW PRIORITY (STANDARD OR PRIORITY): Priority

PROPOSED INDICATION: Treatment of (b) (4) Diabetic Macular Edema (DME)

SUBJECTS < 18 YEARS: No

CONSULTATION REQUEST DATE: July 29, 2010

PDUFA: December 30, 2010

I. BACKGROUND:

Alimera Sciences, Inc. submitted a new drug application NDA 201923 for Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg, on June 28, 2010 to support a labeling claim for the treatment of Diabetic macular edema (DME). Diabetic macular edema, a serious, chronic, debilitating disease, is the primary cause of vision loss associated with diabetic retinopathy. There are no approved drug therapies for the treatment of DME. The standard of care is laser photocoagulation.

To support the approval, the Applicant has provided data from efficacy in two controlled clinical trials (Study C-01-05-001A and Study C-01-05-001B) involving 956 patients which they believe provide sufficient evidence to support the safety and efficacy of Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg for the treatment of Diabetic macular edema.

The most common treatment-emergent adverse events reported in clinical studies with Iluvien, were cataract operation due to cataract (more commonly posterior subcapsular cataracts), and increased intraocular pressure (IOP). Glaucoma and ocular infections may also be associated with the use of corticosteroids.

In both studies that are presented to support this application, a Contract Research Organization (CRO) was used to manage the interactive voice response system to track subjects during the study (e.g subject screen failure, subject entry, follow-up visits, subject participation status). In North America and Europe the CRO was (b) (4) and in (b) (4).

Brief descriptions of the studies inspected (Study C-01-05-001A and Study C-01-05-001B) are provided below:

Protocol C-01-05-001A: A randomized, double-masked, parallel group, multi-center, dose-finding comparison of the safety and efficacy of ASI-001A 0.5 µg/day and ASI-001B 0.2 µg/day fluocinolone acetonide intravitreal inserts to sham injection in subjects with diabetic macular edema (FAME® STUDY)

This was a phase 3, randomized, double-masked, sham injection-controlled, parallel-group, multi-center safety and efficacy study conducted over a 36-month period in subjects with DME. Enrollment was to be stratified by baseline Best Corrected Visual Acuity (BCVA) (≤ 49 , >49 letters) because response to treatment may have been related to the subject's initial visual status. Subjects were to be enrolled and randomized in a 2:2:1 ratio to 1 of 3 treatment

groups: 0.2 µg/day fluocinolone acetonide (FA) intravitreal insert, 0.5 µg/day FA intravitreal insert, or sham injection. The assigned treatment was to be administered to only 1 eye, referred to as the “study” eye. The study was to consist of at least 18 visits and a 3-year post-treatment period and was to be conducted at 49 sites in 7 countries (United States, Canada, 4 countries in the European Union, and India).

The primary objective was to determine if either dose level of FA intravitreal insert is superior to the control group with respect to the proportion of subjects with a ≥ 15 -letter increase in best corrected visual acuity (BCVA) at Month 24 compared to baseline. Secondary study objectives were to 1) choose the optimum dose level of intravitreal FA, 2) compare the 2 dose levels versus the control group at other time points, and 3) evaluate the efficacy of 0.2 µg/day and 0.5 µg/day FA intravitreal inserts in diabetic macular edema (DME) and diabetic retinopathy (DR) using other relevant measures. Safety was also evaluated.

The planned enrollment was to include approximately 450 subjects with a clinical diagnosis of DME. The screening visit was conducted within 21 days of enrollment and established the subject's eligibility. At Visit 2 (Day 0), 1 eligible eye per qualifying subject was to be randomly assigned to treatment, which was administered at that visit. Visits 1 and 2 were to be combined on the same day, if possible. Visits 3 and 4 were to monitor the safety of the treatment procedure. The remaining visits were to be scheduled at Week 6, Month 3, and every 3 months after the Month 3 visit. If progression of edema occurred, the subject was to receive retreatment after 12 months. After retreatment, there were to be 2 post-treatment visits at 1 day and 1 week.

The assessments in this study were to include medical/ophthalmic history; concomitant medications and treatments; adverse events (AEs); clinical labs (HbA1c) and pregnancy testing; vital signs; IOP; slit-lamp examinations; visual acuity (VA); dilated ophthalmoscopy; fluorescein angiography; bilateral fundus photography; optical coherence tomography; contrast sensitivity testing; a validated health-related quality of life (HRQOL) survey; and specular microscopy for endothelial cell counts at selected sites.

To be eligible for the study, subjects (males and non-pregnant females) had to be at least 18 years of age, have a diagnosis of diabetes mellitus (type 1 or type 2), and undergone at least 1 macular laser treatment >12 weeks prior to screening. All subjects were required to provide written informed consent. Eligible subjects assigned to active therapy were to receive a single intravitreal insert of FA (either 0.2 or 0.5 µg/day) in the study eye. Subjects were eligible for retreatment after Month 12 if they experienced vision loss (documented reduction of 5 or more letters in Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity [VA]) or retinal thickening per optical coherence tomography (OCT) (minimum increase of 50 microns at the center of the fovea) as compared to the subject's best status during the previous 12 months.

Protocol C-01-05-001B: A randomized, double-masked, parallel group, multi-center, dose-finding comparison of the safety and efficacy of ASI-001A 0.5 ug/day and ASI-001B 0.2 ug/day fluocinolone acetonide intravitreal inserts to sham injection in subjects with diabetic macular edema. (FAME® STUDY)

The study was conducted at 52 sites in United States, India, and 3 countries in the European Union. Study C-01-05-001B was similar to Study C-01-05-001A in design and conduct.

Two sites were selected for inspection, one domestic and one foreign, due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #/ Site #/ # of Subjects:	Inspection Date	Final Classification
Peter J. Blackburn, M.D. 740 South Limestone UK Department of Ophthalmology and Visual Sciences Lexington, KY 40536	Study C-01-05-001B / Site 001/17	09/20/2010 - 10/04/2010	Pending (Interim classification: VAI)
Sat P. Garg, M.D. All India Institute of Medical Sciences Department of Ophthalmology Ansari Nagar New Delhi, India 11029	Study C-01-05-001A / Site 016/ 45	10/18/2010 - 10/29/2010	Pending (Interim classification: 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 483 and/or preliminary communication with the field (EIR has not been received from the field and complete review of EIR is pending) or Final Classification correspondence has not issued.

1. **Peter J. Blackburn, M.D.**

740 South Limestone
 UK Department of Ophthalmology and Visual Sciences
 Lexington, KY 40536

a. **What was inspected?**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/20/2010 and 10/04/2010.

A total of 20 subjects were screened at this site, 17 subjects were enrolled in the study. Thirteen (13) subjects completed the study at this location. Two subjects were lost to follow up, one subject died due to cerebrovascular accident deemed unrelated to study, and

one subject discontinued the study due to AE (Heart Attack), which was reported to the sponsor.

The inspection included review of records for 17 subjects enrolled in the study. There were three Serious Adverse Events [Subject 100115-Death (deemed unrelated to study); Subject 100117-infected foot ulcer; Subject 100105-Gastric Bypass Surgery during the study]. The following items were reviewed for verification: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Blackburn's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator. The following observations were included on the Form FDA 483:

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. For example:

- a) The review of case report forms and source documents for Subjects 100114, 100115, 100116, and 100117 revealed that source documents were missing for Visit 2 (Visits 1 and 2 were to determine eligibility, randomization and to administer first dose of study drug).

DSI Reviewer Comments: *The study was to consist of at least 18 visits and a 3-year post-treatment period. According to the protocol, Visits 1 and 2 were to be combined on the same day, if possible. Reviewing the CRF shows Visits 1 and 2 were combined on the same day, for Subjects 100114, 100115, and 100117, which was allowed specifically by the protocol. Additionally, the monitor reports from [REDACTED] (b) (4) (EIR Exhibit 22) dated December 20, 2006, July 12, 2007, September 19, 2007 show that source and CRF documents had been reviewed for Visit 2 for subjects 100114, 100115, 100116, and 100117. Based on evaluation of Visit 1 records and other source documents (i.e. randomization logs, drug accountability records), the inspection was able to confirm that subjects met eligibility criteria, that randomization was performed adequately, and the first dose of drug was administered adequately. As such, this finding is unlikely to impact data reliability.*

- b) The review of case report forms and source documents for subjects 100108, 100109, 100110, 100111, 100112, 100113 revealed that source documents were missing for Visit 3. The CI should have retained and maintained the study records. (Visit 3 was to monitor the safety of the treatment procedure by obtaining post-treatment telephone contact, post-treatment medications, adverse events, concomitant treatments)

DSI Reviewer Comments: *The study was to consist of at least 18 visits and a 3-year post-treatment period. The monitor reports from [REDACTED] (b) (4) (EIR Exhibit 22), dated December 1, 2006 and January 29, 2007 show that source and CRF documents had been reviewed for Visit 3 for Subjects 100108, 100109, 100110, 100111, 100112, 100113, and no discrepancies were identified. Additionally, review of source documents at subsequent visits, provide specific evaluation of post-treatment medications, adverse event evaluation of concomitant treatments. As such, this finding is unlikely to significantly impact data reliability.*

Overall DSI Reviewer comments: *Although the clinical investigator failed to maintain the source documents for the above subjects for Visit 2 and 3 according to the investigational plan, the failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation occurred in isolated visits and the information that was supposed to be collected during Visit 2 and 3 has been captured during the previous (during visit 1) or subsequent visits. As such, the observed violations may not have significant impact on data reliability. However the review division may choose to consider analyzing the data from this site using multiple imputations. The recommendation has been discussed with the review division medical officer, and he also concurs that these specific findings, given the mitigating factors summarized above, are unlikely to significantly impact data reliability.*

c. Assessment of data integrity:

Although regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data from the site. Based on the provided EIR for this site and Dr. Blackburn's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Blackburn's site are considered reliable.

2. Sat P. Garg, M.D.

All India Institute of Medical Sciences

Department of Ophthalmology
Ansari Nagar
New Delhi, India 11029

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811 between 10/18/2010 and 10/29/2010.

A total of 49 subjects were screened at this site, 45 subjects were enrolled in the study. Twenty eight subjects completed the study at this location and 17 subjects dropped out.

The inspection included review of records for 49 subjects enrolled in the study. Review of records included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations; subject eligibility; informed consent documentation; test article accountability/disposition; Ethics Committee approvals; monitoring records; case report forms; concomitant medication usage, and adherence to protocol-specified procedures for blinding and randomization. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Sat Garg's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator. The following observations were included on the Form FDA 483:

- i. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. Specifically, protocol deviations had not been reported to the Ethics Committee and to the sponsor in a timely manner. For example:
 - a) The study protocol required subjects to have IOP re-measured within 1 month if IOP was between 22 mm Hg and 30 mm Hg. A subject (Subject # 101605) who had intraocular pressure (IOP) that was between 22 mm Hg and 30 mm Hg (26 mm Hg and 28 mm Hg) on two occasions had no IOP re-measurement within a month.
 - b) The study protocol required measuring optical coherence tomography (OCT) at various time intervals. Subject # 101623: did not complete optical coherence tomography (OCT) in OD for visit 6.
- Subject # 101640/ Subject # 101624: use of prohibited medication/therapy (posterior subtenon injection of triamcinolone) in the study eye that had potentially confounding effects on DME.

DSI Reviewer Comment: Dr.Garg adequately responded to the inspection findings in a letter dated November 19, 2010. Even though, the clinical investigator failed to assure timeliness of reporting of unanticipated problems involving risk to human subjects to the IRB, all the protocol deviations have been reported to the sponsor and appear in the NDA.

c. Assessment of data integrity:

While the FDA inspection revealed regulatory violations of clinical investigator obligations in the conduct of the study, these are considered isolated in nature and unlikely to significantly impact data reliability. The data derived from Dr. Sat Garg's site appear reliable in support of the NDA.

Note: Observations noted above are based on communications with the field investigator; another inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites, one domestic and one foreign, were inspected in support of this application. Although regulatory violations were noted at both of these sites, given the nature of the findings, it is unlikely that data reliability would be impacted. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

The preliminary classification of Clinical Investigator inspections of Drs. Blackburn and Garg are Voluntary Action Indicated (VAI).

Note: Final classification for both sites is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

KASSA AYALEW
12/01/2010

TEJASHRI S PUROHIT-SHETH
12/01/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201923	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Iluvien Established/Proper Name: fluocinolone acetonide intravitreal insert Dosage Form: intravitreal insert Strengths: 0.19 mg		
Applicant: Alimera Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: June 30, 2010 Date of Receipt: June 30, 2010 Date clock started after UN: n/a		
PDUFA Goal Date: December 30, 2010	Action Goal Date (if different):	
Filing Date: August 13, 2010	Date of Filing Meeting: July 29, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3, new dosage form		
Proposed indication(s)/Proposed change(s): Treatment of diabetic macular edema		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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)	
Collaborative Review Division (if OTC product):		

List referenced IND Number(s): IND 72056				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
<p>PDUFA and Action Goal dates correct in tracking system?</p> <p><i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></p>	X			
<p>Are the proprietary, established/proper, and applicant names correct in tracking system?</p> <p><i>If not, 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.</i></p>	X			
<p>Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?</p> <p><i>If not, ask the document room staff to make the appropriate entries.</i></p>	X			
Application Integrity Policy	YES	NO	NA	Comment
<p>Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>		X		
<p>If yes, explain in comment column.</p>				
<p>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</p>				
User Fees	YES	NO	NA	Comment
<p>Is Form 3397 (User Fee Cover Sheet) included with authorized signature?</p>	X			
<p><u>User Fee Status</u></p> <p><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 UN letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p> <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 </p>			
<p><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></p>	<p>Payment of other user fees:</p> <p> <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears </p>			
<p>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</p>				

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?			X		
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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
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))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X			
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
NDA 21737	Retisert (fluocinolone acetonide)	Orphan Drug	April 8, 2012		
<i>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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 years		X			
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>					

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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
<p>If electronic submission, does it follow the eCTD guidance¹? If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including:</p> <p><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)</p> <p>If no, explain.</p>	X			
<p>Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p>			X	
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>				

Forms and Certifications				
<p><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), 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></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>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...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>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 reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>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?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Submitted separately to OSE 7/15/10, SDN #6
Prescription Labeling	<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)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
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? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
REMS consulted to OSE/DRISK?		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			X	

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 9/2/08 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/4/10 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7/29/10

BLA/NDA/Supp #: 201923

PROPRIETARY NAME: Iluvien

ESTABLISHED/PROPER NAME: fluocinolone acetonide

DOSAGE FORM/STRENGTH: intravitreal insert

APPLICANT: 0.19mg

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of diabetic macular edema

BACKGROUND: Alimera Sciences submitted their New Drug Application on June 30, 2010, and requested a priority review. The request is based on the need for drugs that are intended to treat serious or life-threatening conditions or offer major advances in treatment where no adequate therapy exists. Diabetic macular edema (DME) is a serious, chronic, debilitating disease and is the primary cause of vision loss associated with diabetic retinopathy. Currently, there are no approved drug therapies for the treatment of DME.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dean	Y
	CPMS/TL:	Dillon Parker, M.	N
Cross-Discipline Team Leader (CDTL)	Boyd, W.		Y
Clinical	Reviewer:	Nevitt, M.	Y
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Bergman, K.	Y
	TL:	Bonapace, C.	Y
Biostatistics	Reviewer:	Izem, R.	Y
	TL:	Wang, Y.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Chen, C.	Y
	TL:	Schmidt, W.	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (for BLAs/BLA efficacy supplements)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Matecka, D.	N
	TL:	Ng, L.	Y
Quality Microbiology (for sterile products)	Reviewer:	Fong, S.	Y
	TL:	McVey, J.	N
CMC Labeling Review (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Dorch, B.	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Ayalew, K.	Y
	TL:		

Other reviewers		
Other attendees: CMC Branch Chief ONDQA PM Statistics Division Director Clinical Reviewer Acting Director (DAIOP)	Ocheltree, T. Cuff, A. Lin, D. Harris, J. Chambers, W.	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Cataract issue</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <p>Reason: AC meeting not scheduled because original application lacked visual acuity assessments in the submitted dataset (i.e., acuity beyond 24 months) considered necessary for the application's risk-benefit assessment</p>
<ul style="list-style-type: none"> • 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? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>Comments:</p>	
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</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>BIOSTATISTICS</p> <p>Comments:</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</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><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Quality Microbiology (for sterile products)</p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Facility Inspection</p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Facility/Microbiology Review (BLAs only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CMC Labeling Review (BLAs/BLA supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Wiley A. Chambers, MD, Acting Director, DAIOP	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • 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 DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	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.

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/s/

JANE A DEAN
10/26/2010